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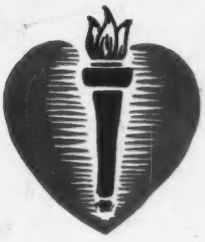

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Controlled Observations on the Effect of Low Sodium Dietotherapy in Essential Hypertension

By A. C. Corcoran, M.D., Robert D. Taylor, M.D., and Irvine H. Page, M.D.

The effectiveness and practicality of low sodium diets are tested in groups of in- and outpatients. The data indicate that roughly one-fourth with severe essential hypertension can respond favorably to prolonged restriction of sodium intake to less than 0.5 Gm. daily. The rice diet is found to be in effect a simple low sodium diet. Under the conditions of outpatient practice, low sodium dietotherapy is usually impractical and must be controlled by frequent analyses of urinary sodium.

RENEWED use of diets of low sodium content in essential hypertension has led to controversy both as to their effectiveness and as to the origin of the practice.

Uncertainty of attribution is maintained by strained interpretations from the past 85 years or more. Thus, Karrell gives no indication that he was concerned either with arterial pressure or with electrolyte intake. Probably the first specific use of chloride restriction—with an attendant deprivation of sodium—in essential hypertension, was that of Ambard and Beaujard.[1] But the number and selection of cases and method of study leave much to be desired. Consequently, the reports of Allen[2] and Allen and Sherrill[3] in 1922 on the usefulness in essential hypertension of diets poor in sodium chloride is a point of departure for this avenue of treatment. The hiatus between their study and the current use of low-sodium diets, interrupted briefly by Addison,[4] has been commented on by Allen.[5] It is largely attributable to the fact that, until recently, any practical low sodium diet of average protein content contained about 0.8 Gm. of sodium, a level of restriction which does not often have a definite effect on arterial pressure.[6]

The revival of sodium restriction is based on three types of study. One is the hypertension and nephrosclerosis Selye elicited in rats by treatment with excess sodium chloride and injection of desoxycorticosterone. A major clinical contribution has been the Kempner rice diet.[7] His insistence on the specificity of rice, the diversity of his clinical material and his lack of controlled observations are reminiscent of European studies 50 years ago and have been so criticized by Ayman.[8] Nevertheless, the rice diet seems, by weight of numbers at least, to show some effectiveness in hypertensive disease. For a more critical study, in which the only change in the diet was deprivation of sodium, we are indebted to Grollman and Harrison.[9] Their observations were confirmed and extended by Bryant and Blecha[10] in a much larger series, but under much less adequate conditions of observation. Relevant also are the observations of Perera and Blood[11] who showed that, as a group, patients with essential hypertension tend to retain sodium unduly and tend also to show increased arterial pressure when sodium is given in excess.

These and other numerous observations on

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TABLE 1.—*The Course of the Inpatient Study. Types of Patients Treated and Diets Used.*

No.	Age	Sex	Diagnosis	High Sodium		Low Na	
				Diet	Duration (weeks)	Diet	Duration (weeks)
1	46	F	Ess. Hyper.	1800 C	4 (C)	L	2 (1)
2	65	M	As. Hyper.	CLS	3 (C)	L	3 (1)
3	47	M	Ess. Hyper.	Ward	3 (C)	L	12 (1)
4	49	F	Ess. Hyper.	1000 C	4 (C)	L	6 (1)
						R	4 (2)
5	41	F	Ess. Hyper. M.	Ward	3 (C)	R	8 (1)
						L	5 (2)
6	48	F	Ess. Hyper.	Ward	3 (C)	L	7 (1)
						R	5 (2)
7	50	F	Ess. Hyper.	Ward	2 (C)	L	4 (1)
8	46	F	Ess. Hyper.	Ward	2 (C)	L	74*(1)
9	54	F	Ess. Hyper.	Ward	3 (C)	L	6 (1)
				Ward	5 (2)	L	6 (3)
				L + 4.7 Na	4 (4)	L	3 (5)
10	52	M	Ess. Hyper.	1000 C	2 (C)	L	2 (1)
				L + 4.8 Na	2 (1)		
11	46	M	Ess. Hyper. M.	Ward	14 (C)	R	16 (1)
						R + 30 Gm. P	12 (2)
						R + 60 Gm. P	5 (3)
				R + 60 Gm. P + 3.3 Na	3 (4)		
				L + 3.3 Na	4 (5)		
12	45	M	Ess. Hyper. M.	Ward	2 (C)	L	12 (1)
						L	8 (2)
				L + 7 Na	6 (3)	L	1 (4)
						L	7 (5)
				L + 7 Na	1 (6)		
				L + 7 Na	5 (7)		
13	38	F	Ess. Hyper. M.			R	6 (1)
				R + 2.4 Na	4 (2)	R	1 (3)
						L	8 (4)
				Ward	6 (5)		
				5 Na + 2.4 Na	3 (6)		
				L + 7.2 Na	2 (7)		
				L + 7.2 Na	12 (8)	R	1 (9)
						R	5 (10)
						R	4 (11)
						L	11 (12)
				2.0 Na + 1.6 Na	(13)		
				2.0 Na + 4.1 Na	(14)		
				2.0 Na + 4.8 Na	(15)		
				2.0 Na + 4.8 Na	(16)†		
				2.0 Na + 4.8 Na	(17)		
14		M	Ess. Hyper. M.	Ward	4 (C)	R	4 (1)
						R	4 (2)
						R + 0.4 Na[a]	2 (3)
						R + 0.4 Na[b]	3 (4)
						R + 0.4 Na	2 (5)
						R + 0.4 Na[c]	2 (6)
						R + 0.4 Na[d]	3 (7)
				R + 0.4 Na	3 (8)	L + 90 Gm. P	1 (9)
						L + 40 Gm. P	2 (10)

Types of patients treated were Ess. Hyper., essential hypertension (M, malignant phase); and As. Hyper., arteriosclerotic hypertension. Control diets are indicated by calories, e.g., 1800 C; by CLS, cardiac low salt diet containing about 1 Gm. Na; or by Ward, ward diet.

(*Continued on next page*)

LEGEND TABLE 1 (Continued)

Indications in test period diets are: Numerals in parentheses refer to successive intervals on high or low sodium intakes. R = rice diet; P = protein as Lonalac. L refers to the Lonalac diet containing an estimated 0.2 Gm. Na. Sodium supplements (Gm. of enteric-coated sodium chloride) are indicated by such entries as 4.7 Na. The dagger (period 16, patient 13) refers to the intramuscular administration of cortate in propylene glycol, 10 mg. daily. Superscript letters (patient 14) indicate as follows: [a]choline chloride, 11.5 Gm. daily; [b]methionine, 6.0 Gm. daily; [c]Proteinum, 68 Gm. daily; [d]Protolyzate, 90 Gm. daily. The sodium content of Protolyzate is equivalent to 1.6 Gm. daily in the amount given. In period 9 this patient was given 0.2 Gm. Lonalac diet with the supplement increased to 90 Gm. protein per day; in period 10, the supplement was decreased to 40 Gm. protein per day.

For patient 8, the asterisk notes the fact that the inpatient observations, extending over 74 weeks, were discontinuous and made in several readmissions, although dietary control (estimated from urinary sodium) was maintained throughout the course.

For patient 12, low sodium periods 1 and 2 are separated by some months, during which the patient was at home; period 4 is separated from period 5 because it is the first week of sodium restriction and demonstrates the lag in response; period 6 is separated from period 7 because it is the first week of sodium administration and shows a similar lag.

Patients 5, 12 and 13 had been treated with pyrogenic bacterial extracts prior to the low sodium observations. This accounts for the brevity of the control period in patient 12, there being numerous observations under pyrogen, and the absence of a definite control in patient 13: the place of a control period in patient 13 is taken by five periods of high sodium treatment. In patient 13 also, period 10 is separated from period 11 because of a fracture of the femur which occurred at the end of the fifth week of period 10. Patient 14 went into uremia at the completion of period 10.

low sodium diets, including the rice diet, need not be cited in more detail, since they have been carefully reviewed.[12, 13] However, few of these studies carry full conviction. There is doubt, on the part of either the author or the reader, as to the reality of the change or the lack of change (Chasis, Goldring and associates[14]) or uncertainty in the adequacy of the dietary control or both, and added to these are the psychologic imponderables which flow from a more or less drastic revision of the patient's mode of life.

Many of the problems thus left open have been posed editorially.[15] The purpose of this report is to resolve some of these and particularly the following issues: (1) does sodium restriction, as such, effectively decrease arterial pressure in essential hypertension and, if so, in roughly what proportion of patients? Granting the usefulness of sodium restriction, (2) does the rice diet—which, in our hands, in a small series had proved quite unavailing—depend for what effect it has on sodium restriction or has it some other basis? (3) What is the minimum effective sodium restriction and how long must it be maintained before it can be determined whether or not a patient is to respond to such treatment? (4) What is the practicality of low sodium dietotherapy under the conditions of outpatient office practice, in contrast with those prevailing in wards equipped for special studies?

With particular regard to this last problem, we shall present our data in two groups, respectively, the inpatient and outpatient series.*

I. INPATIENTS

1. *Method.*

The course of this study is summarized in table 1. Four of the 14 patients listed there had essential hypertension in the malignant phase; patient 5 had been treated with pyrogen before the course of dietotherapy, but with incomplete remission of her evidences of rapidly advancing and soon fatal disease; patients 12 and 13 had obtained remissions of the malignant syndrome by pyrogen treatment before beginning dietary treatment.

During the control periods, which ranged from 2 to 14 weeks, the diets given were ward diets (containing about 3 Gm. of sodium daily) or similar diets with caloric and consequently partial sodium restriction. The control periods in patient 13 follow rather than precede the first period of sodium restriction. Diets used in treatment or in assessing the value of treatment were (a) the 0.2 Gm. sodium diet in which the

* For careful attention to the outpatient series we are grateful for the assistance of Miss E. M. Davy, R. N., who assumed the major duties of this study, and to Miss Marjorie Curry, B.Sc., who instructed the patients in their diets.

TABLE 2.—*Cardiovascular Changes on Low Sodium Diets (Inpatients).*

No.	Period	Urine Na Gm/24 hrs.	B. P.	Fundi	Heart size	ECG	Other	Response
1	Control	—	182/110	32122	5	1		
	(1)	0.12	189/109	32000	—	1	Subsequent Improvement	0 (L)
2	Contr.	—	182/106	23030	15	3		
	(1)	—	178/105	23020	15	3		0 (L)
3	Contr.	2.3	199/121	32000	10	2		
	(1)	0.4	206/130	32000	12	2		0 (L)
4	Contr. q	—	212/128	22210	8	2.5		
	(1)	0.26	208/130	22010	8	2.5		0 (L)
	(2)	0.28	206/126	22000	8	2.5		0 (R)
5	Contr.	1.8	193/122	22110	8	3		
	(1)	0.22	195/126	22001	8	3		0 (R)
	(2)	0.28	204/134	22110	8	3		0 (L)
6	Contr.	0.9	208/123	22210	25	2.5		
	(1)	0.37	219/127	22110	20	2		0 (L)
	(2)	0.3	202/119	22210	25	2		0 (R)
7	Contr.	5.0	206/129	32111	15	2		
	(1)		198/120	22010	12	2	Subsequent Improvement	0 (L)
8	Contr.	1.6	217/123	22120	−10	2		
	(1)	0.16	190/112	22110	−10	2	Subsequent Improvement	+ (?) (L)
		0.10	187/113	22110	−10	2	Subsequent Improvement	+ (?) (L)
		0.38	220/118	22100	−10	2	Subsequent Improvement	
		0.11	220/122	22100	−10	2	Subsequent Improvement	
		0.05	198/115	22000	−10	2	Subsequent Improvement	
9	Contr.	—	203/121	02000	+10	0		
	(1)	—	176/107	02000	+10	0	Subsequent Improvement	+ (L)
	(2)	3.0	166/113	02000	+10	0	Headache	+ (L + Na)
	(3)	0.34	165/99	02000	+10	0	Subsequent Improvement	+ (L)
	(4)	2.2	181/103	02000	+10	0	Headache	+ (L + Na)
	(5)	0.5	160/99	02000	+10	0	Subsequent Improvement	+ (L)
10	Contr.	1.0	176/113	22000	+10	0		
	(1)	0.6	156/100	22000	+10	0		+ (?)
	(2)	4.2	166/105	22000	+10	0		+ (?) (L + Na)
11	Contr.	—	182/119	24211	+15	2		
	(1)	0.3	177/121	24111	+12	1		0 (R)
	(2)	0.2	173/117	24110	+12	1		0 (R + P)
	(3)	0.1	183/126	24100	+12	1		0 (R + P)
	(4)	2.2	190/126	24000	+12	1		0 (R + P + Na)
	(5)	2.2	190/129	24000	+12	1		0 (L + P + Na)
12	Contr.	3.0	186/118	23101	+15	3		
	(1)	0.3	162/105	23101	+15	3		+ (L)
	(2)	0.49	161/105	22000	+18	3		+ (L)
	(3)	5.6	186/116	22000	+18	3		+ (L + Na)
	(4)	0.4	180/115	32000	+12	3		
	(5)	0.45	152/101	32000	+10	3		+ (L)
	(6)	0.8	158/101	32000	+10	3		
	(7)	6.1	181/113	32000	+10	3		+ (L + Na)
13	(1)	0.2	141/96	12000	−10	3		100 + (R)
	(2)	3.0	177/115	12011	−10	3		99 + (R + Na)
	(3)	0.1	131/100	12000	−10	3		97 + (R)
	(4)	0.15	127/88	02000				104 + (L)
	(5)	4.3	142/92	02000				108 + (W)
	(6)	7.4	132/85	12000	−10	3		110 + (?) Na

TABLE 2.—*Cardiovascular Changes on Low Sodium Diets (Inpatients)* (Continued)

No.	Period	Urine Na Gm/24 hrs.	B. P.	Fundi	Heart size	ECG	Other	Response
	(7)	7.5	160/102	22000	−10	3		110 + (L + Na)
	(8)	7.5	176/114	12000				119 + (L + Na)
	(9)	0.6	170/110	12000				117
	(10)	0.03	123/90	02100				115 + (R)
	(11)	0.1	128/84	02100				+ (R)
	(12)	0.17	117/78	02000	−10	3		105 + (L)
	(13)	3.0	129/88	02000				110 + (?) (Na)
	(14)	5.1	147/106	12100				117 + (Na)
	(15)	6.7	155/108	12100	−10			119 + (Na)
	(16)	5.8	170/114	12000	−10	3	(Cortate)	+
	(17)	6.0	161/107	12000	−10	3		115 +
14	Contr.	2.0	206/125	32201	+20	1		135
	(1)	0.23	202/124	32011	+10			127
	(2)	0.19	177/111	22000	+5	0	Subsequent Improvement	122 + (R)
	(3)	0.46	155/94	22000			Subsequent Improvement	121 + (R)
	(4)	0.39	168/100	22000	+10	0	Subsequent Improvement	121 + (R + C)
	(5)	0.58	156/98	22000			Subsequent Improvement	120 + (R + M)
	(6)	0.59	161/100	22000			Subsequent Improvement	118 + (R)
	(7)	0.67	153/97	22000	+20	0	Subsequent Improvement	125 + (R + Pn)
	(8)	1.61	173/107	32011		0	Subsequent Worse	131 + (P + Pe)
	(9)	0.5	202/138	32011	+25	0	Subsequent Worse	132 0 (L)
	(10)	0.5	227/130	32010		0	Subsequent Worse	128 0 (L)
15	Contr.		203/134					CLS
	(1) (6 wk)	1.8	188/116				(Fever 102 F)	Pyr.
	(2) (2 wk)	0.5	195/124					(L)
	(3) (3 wk)	0.15	178/105				(Fever 102 F)	Pyr. + L
	(4) (3 wk)	1.6	189/112				(Fever 103 F)	Ward
	(5) (6 wk)	0.36	191/107				(Fever 102.6 F)	Pyr. + L

Patients' numbers listed in first column correspond to those of table 1. Patient 15 is added to illustrate the interaction of sodium restriction and pyrogen treatment. The mean urinary sodium excretion is expressed in Gm. per 24 hours for control period and each period of observation (second and third columns). The fourth column indicates means of arterial pressures for each period, the fifth the estimation of vascular changes in the optic fundi, the sixth the estimate of cardiac size by the method of Ungerleider and Gubner and the seventh the estimate of electrocardiographic abnormality (on a scale of 1 to 4 plus). In the last column are indications of the nature of dietotherapy and responses thereto (0 = none, + = favorable) and body weight in pounds for cases 13, 14 and 15. Abbreviations as in table 1, with the additions C, choline; M, methionine; Pn, Proteinum; Pe, Protolyzate; Pyr, pyrogen.

protein is made up in part in Lonalac* (b) the same with added tablets of sodium chloride†; (c) the rice diet as originally prescribed or (d) with protein added in the form of Lonalac; (e) a diet calculated to contain 2 Gm. sodium and (f) the rice diet with special supplements as provided to patient 14.

Blood pressures were measured at rest regularly each morning and evening. The averages presented in table 2 are the means of these daily observations, from which, however, the first three to five days of hospitalization are excluded. Urine sodium content was determined daily or twice a week by the method of Hoffman and Osgood[16]; the values shown in table 2 are means of these observations. The methods of estimating fundoscopic change and of grading the electrocardiogram have been presented elsewhere,[17] where also are described the procedures used in the Addis test of urinary con-

* We are indebted to the Mead Johnson Co., Evansville, Ind., for generous supplies of Lonalac.

† We acknowledge the donation by Dr. K. G. Kohlstaedt, Lilly Laboratory for Clinical Research, Indianapolis, Ind., of enteric-coated tablets of sodium and ammonium chloride and of placebo.

TABLE 3.—*Effect of Diets on Addis Test and Sediment Count*

Patient No.	Period Diet	Duration Weeks	Sp. Gr.	Prot. Gm.	RBC mils.	Casts thous.	Urine Na Gm./24 hrs.
1	Contr.		1.022	0	0.3	100	
	(1) L	4	1.019	L	0.6	0	0.15
2	Contr.		1.016	0.4	L	180	High
	(1) L	12	1.018	0.6	0	170	Low
5	Contr.		1.020	0	0	0	1.8
	(1) (R)	4	1.019	0	L	500	L
6	Contr.		1.018	0			0.9
	(1) L	7	1.020	0	0.6	0	0.4
	(2) (R)	5	1.008	0	0.3	0	0.3
7	Contr.		1.023	0	0.1	30	5.0
	(1) L	30 (DPD)	1.026	0	0	12	0.1
8	Contr.		1.029	0	L	18	1.6
	(1) L	4	1.021	L	1.3	140	0.16
	(1b)	10	1.019	0	0.7	0	0.1
	(1c)	20	1.023	0	L	10	0.38
	(1d)	36	1.026	0	L	140	0.11
	(1f)	74	1.025	0	0	67	0.05
9	Contr.		1.021	0	0.7	14	High
	(1) L	5	1.021	0	L	60	Low
	(2) Ward	3	1.028	0	0.9	0	3.0
	(3) L	3	1.025	0.1	0.4	65	0.3
	(4) (L + Na)	3	1.025	0.1	1.2	28	2.2
11	Contr.		1.020	0.4	0.6	170	High
	(1) (R)	6	1.019	0.4	0.3	65	0.3
	(2) (R)	12	1.007	L	0.1	35	
	(1) (R)	12	1.019*	0.3	0.3	70	L
	(1) (R)	16	1.008	0.5			
	(2) (R + P)	2	1.016	0.3	1.1	60	
	(2) (R + P)	5	1.015	0	0	6	L
	(3) (R + P)	1	1.018	0	0	60	0.1
	(3) (R + P)	2	1.017	0	0	20	
	(3) (R + P)	4	1.016	0.5	0.5	20	
	(4) (R + P + Na)	3	1.017	L	0.1	10	2.2
	(5) (L + Na)	4	1.016	0	0	100	2.2
12	Contr.		1.025	0.16	0.3	120	3.0
	(1) L	10	1.022	0.14	L	200	0.3
	(3) (L + Na)	4	1.023	0.1	0.7	75	5.6
	(5) L	4	1.028	0.16	L	25	0.45
13	(1) (R)	4	1.015	0.4	0.1	5	L
	(2) (R + Na)	14	1.019	0.0	0.0	0	3.0
	(4) L	6	1.020	0	0.4	0	0.1
	(6) (Ward)	3	1.024	0	0	0	7.4
	(7) (L + Na)	2	1.024	0	0.8	39	7.5
	(8) (L + Na)	10	1.025	0	0.3	0	7.5
	(9) (R)	1	1.018				0.6
	(10) (R)	3	1.013	0.1	1.8		0.03
	(12) L	2	1.010	0.1	1.2	0	0.2
	(14) (2.0 + 4 Na)		1.022	0.1	0	0	5.1
	(17) (2.0 + 4.8 Na)		1.020	0.2	0	0	6.0
14	Contr.		1.010	6.7	30	100	2.0
	(1) (R)	3	1.007	2.3	1.5	0	0.2
	(2) (R + Na)	4	1.008	1.9	1.5	0	0.2
	(3) (R + Na)	2	1.008	1.1	3.5	0	0.4

TABLE 3—*Effect of Diets on Addis Test and Sediment Count* (Continued)

Patient No.	Period Diet	Duration Weeks	Sp. Gr.	Prot. Gm.	RBC mils.	Casts thous.	Urine Na Gm./24 hrs.
	(4) (R + Na)	2	1.008	1.6	1.0	0	0.4
	(8) (R + Na)	3		3.4	1.2	300	1.6
	(10) (90.2)	2		3.3	2.2	48	0.5

Maximum urinary nonprotein specific gravity (Sp. Gr.) by Addis concentration test; proteinuria in Gm. per 24 hours; hematuria in millions red blood cells per 12 hours and casts in thousands; estimated coincident urinary sodium content in Gm. per 24 hours; by periods (numerals in parentheses) and diets as detailed in table 1.

* Indicates administration of pituitrin during the night of a concentration test in patient no. 11, while on rice diet.

centration, the count of the urinary sediment and the measurements of specific renal functions.

2. *Results.* (*Table 2*)

Urinary sodium content averaged less than 0.5 Gm. daily during the periods of restriction. The effort was made in most cases to keep it at about the 0.2 Gm. level.

Arterial Pressure. No significant change occurred in 9 of the 14 patients (cases 1–7, 10, 11) during sodium restriction; pressures were decreased by diet in 5 patients (cases 8, 9, 12–14). The response in patient 8 is equivocal; the control period is short and the change, although statistically highly significant, is not large and, in spite of continued dietary restriction, pressures as high as those of the control period were observed during some of her brief readmissions to hospital. But, in 4 of the 14 patients, the responses are unquestionable in view of their magnitude and of the sequences of change of pressure with changing sodium alimentation.

Included in the table are data from one patient (case 15) which demonstrate the concurrent effects of pyrogen and low sodium treatments. Comparison of the control period with the low sodium, pyrogen-free period (2) shows a significant effect of sodium restriction on arterial pressure; the pressures during period (3) on pyrogen with low sodium (0.2 Gm. sodium diet) are lower than during period (1) on pyrogen alone, although the means of the maximum daily fevers are the same for the two periods.* Period (3) of combined treatment is followed by period (4) of more intense treatment with pyrogen and with a rise in the mean of the fever and the omission of sodium restriction is associated with an increase in arterial pressure. However, this difference may have been caused by increasing resistance to pyrogen treatment, since a subsequent period of combined treatment (5) fails to show any advantage from sodium restriction.

Other Cardiovascular Functions. Fundal abnormalities regressed during low sodium treatment in 8 patients (cases 1, 2, 4, 7, 8, 11–14) of whom 5 (cases 1, 2, 4, 7, and 11) showed no response of arterial pressure. Hemorrhages and exudates, present at the outset in patient 12, did not recur during sodium re-alimentation, so that in this case the fundal remission may have been nonspecific. However, the sequences of change in patients 13 and 14 indicate that the remissions were dependent on sodium restriction.

Decreased heart size attributable to sodium restriction was observed only in patient 14, in whom also there was electrocardiographic evidence of improved cardiac status.

Symptomatic improvement was observed in patients 1, 7, 8, 9, and 14, while in the others symptoms were either initially absent or did not change during treatment. Relief of symptoms by treatment was shown in patients 9 and 14.

Renal Functions. (a) Addis Test and Sediment Count (Table 3). The changes in concentrating power observed in patients 1, 2, 6, and 7 were probably insignificant. The sequences of change in patients 9 and 12, whose pressures showed responses to diet, were not related to changes in arterial pressure, although they

* Difference of means/standard error of the differences: between periods (0) and (2), 3.7 systolic and 3.8 diastolic; between periods (1) and (3), 2.6 systolic and 3.4 diastolic; between periods (3) and (4), 3.4 systolic and 2.4 diastolic.

suggest improvements attributable to sodium restriction. The changes in urinary specific gravity observed during treatment with the rice diet were of special interest. One patient (case 6) showed no change in five weeks' treatment; decreases were observed in patients 11, 13 and 14. The decrease in patient 11 was "apparent" rather than real, since a test of concentrating power by combining water deprivation with injection of pituitrin restored specific gravity to the pretreatment level. The same would probably apply to patient 13.

TABLE 4.—*Effect on Specific Renal Functions*

Patient No.	Period	Diet	Duration weeks	C. urea per cent normal	RBF cc./min.	GFR per 1.73 m.	Tm_{PAH} mg./min.
3	Contr.	Ward			428	49	24
	1	L	12			63	19
5	Contr.	Ward		28	348	58	36
	1	R	6	26	329	56	37
6	Contr.	Ward			758	87	44
	1	L	7		515	104	50
	2	Rice	4		633	84	38
7	Contr.	Ward			506	86	56
		L	4		661	72	56
8	Contr.	Ward		76	704	93	73
	1a	L	4	68			
	1b		10	87	724	85	71
	1d		36		700	85	49
	1f		74		640	90	49
9	Contr.	Ward	5	80			
	(1)	L	5	66	736	85	40
	(3)	L	4		1030	106	56
	(4)	L + Na			1170	117	62
11	Contr.	Ward	2	40	354	45	25
	Contr.	Ward	12	36		65	35
	(1)	Rice	16		268	38	22
	(2)	Rice + 30 Gm. P	5		366	45	24
	(3)	Rice + 60 Gm. P	4		316	45	27
	(5)	L + Na	4		305	52	27
12	Contr.	Ward		71	763	94	67
	(1)	L	10	67	749	98	47
	(2)	L	4		710	119	39
	(3)	L + Na	5		863	93	61
	(5)	L	6	75			
	(7)	L + Na	5		763	106	66
13	Contr.				536	64	47
	(4)	L	4		930	83	56
	(11)	Rice	4		626	59	63
	(12)	L	3		652	63	58
	(17)	L + Na	3		893	113	64
14	Contr.	Ward		21	169	23	18
	(1) (R)		3	20			
	(2) (R)		3	16	161	25	8.6
	(3) (R)		2		116	18	10
	(4) (R) + C		3		116	23	8.5
	(5) (R) + M		2		123	20	9.3
	(7) (R) + Pn		3		142	24	9.2
				(Bl. Ur. 75)			

Dietotherapy and the renal functions of urea clearance, renal blood flow calculated from the plasma clearance of *p*-aminohippuric acid (PAH), glomerular filtration (estimated from plasma clearance of mannitol) and tubular excretory capacity (Tm) for PAH. Measurements of functions were made usually at the end of each succeeding dietary period.

TABLE 5.—*Course and Results of Study in Outpatients*

No.	Diagnosis	Diet	Weeks	B.P. mm. Hg	Urine Na Gm./24 hrs.	Course
1	Ess. Hyper. M.	L + Na	4	196/134	3.2	
		L	10	221/151	1.6	Died
2	Ess. Hyper. M.	L + Na	4	196/134	2.0	
		L	12	212/146	0.5	
		L	4	227/148	0.3	Died
3 (no. 9 Table 1)	Ess. Hyper.	L	86	166/98	0.46	
4	Ess. Hyper.	L + Na	5	183/97	3.1	
		L	20	151/82	1.2	
		L + Na	14	163/88	2.0	
		L	26	156/87	1.5	
		Full	9	183/97	3.4	
5	Ess. Hyper.	L + Na	4	206/137	3.0	
		L	13	190/129	0.5	
		L	8	199/134	1.5	
		L	35	185/135	1.0	
		Full	16	199/133	2.9	
6	Ess. Hyper.	L + Na	3	198/105	1.9	
		L	15	177/99	0.6	
		Full	12	201/113		
7	Ess. Hyper.	L + Na	6	157/104	3.3	
		L	20	157/104	2.5	Died
8	Ess. Hyper.	L + Na	4	161/108	2.4	
		L + Na	10	145/98	1.7	
		L	32	132/90	1.4	
		L + Na	6	167/107	2.1	
		Full	3	169/111	4.0	
		0.5 Gm. Na	14	135/93	2.2	
9	Ess. Hyper.	L + Na	3	197/108	3.6	
	Chr. Pyeloneph.	L	20	140/87	0.6	
10	Ess. Hyper.	L + Na	4	170/118	2.7	
		L	12	161/108	0.7	
		L + Na	13	153/105	1.6	
		0.5 Gm. Na	28	155/110	1.8	
11	Ess. Hyper.	800 C	4	189/100	1.8	
		Rice	4	179/101	0.05	
		Rice	17	174/97	1.5	
12*	Ess. Hyper. M.	Full	10	211/127 ± 12/8	3.5	Died
		L + Na	4	195/129 ± 8/7	0.56	
13	Ess. Hyper.					
	39†			174/120	(mean 1.6)	
	19†			170/117	(mean 0.34)	

Summary of observations on low sodium dietotherapy in outpatients. Diagnosis has the connotation indicated in table 1, as also the abbreviations indicating diet. Added sodium in every case was 6 Gm. sodium chloride Blood pressures are averages during the periods of the weekly or biweekly means of several determinations. Urinary Na is averaged over the periods as in table 1. Specific averages of blood pressures at two levels of urinary sodium are shown for patients 12 and 13.

* During periods when urine greater in Na than 0.3 Gm. (mean 1.0), blood pressure was 200/130 ± 15/8. During periods when urine Na less than 0.3 (mean 0.17) blood pressure was 190/128 ± 5/8. The difference in systolic pressures between the two groups of periods of 10 mm. Hg is statistically significant (difference/standard error of difference = 3.3).

† Numbers of observations at urinary Na levels greater and less than 0.5 Gm. per 24 hours.

(b) Urinary Protein and Sediment. Patients 11, 13 and 14, whose pressures responded favorably, all showed decreased proteinuria during sodium restriction. The changes in cast count were irregular; casts decreased in patients 1, 11 and 14, were unchanged in patients 2, 6, 7 and

13, and, were increased during sodium restriction in patients 5, 8 and 9. Correlation between decreased hematuria and sodium restriction could be shown in patient 14, in whom a favorable response was obtained.

(c) Specific Renal Functions (Table 4). The functions of blood flow, glomerular filtration and maximum tubular secretion of *p*-aminohippurate (PAH) were altered irregularly. Blood flow seemed to be decreased by low sodium treatment in 3 patients (cases 6, 11 and 14) and increased in 2 (cases 9 and 13, and possibly, in another, case 7). Glomerular filtration was unchanged in 6 patients and decreased in 2 (cases 11 and 14). Tubular secretory capacity was decreased in 5 patients (cases 3, 8, 11, 12 and 14) and unchanged in 5. Decreases in this function during treatment seem attributable to progress of the disease rather than to sodium restriction or protein lack; however, in 2 patients (cases 11 and 14) an increase of renal blood flow followed provision of extra protein during administration of a rice diet.

II. Outpatients

1. *Method*

The regimes used in these 13 patients were (a) the 0.2 Gm. sodium diet in 11, (b) the rice diet in 1 and (c) the 0.5 Gm. sodium diet in 2. The low sodium regimes were instituted for four to six weeks of control observation during which the patients were given enteric-coated tablets of sodium chloride in a dose of 6 Gm. daily. These were exchanged for identical tablets containing ammonium chloride or a placebo, which in turn were later withdrawn. Blood pressures were taken at rest in the sitting position. Values reported are the means of three to five such measurements and those noted in the table are means of several of these values. The usual studies (electrocardiogram, x-ray films of the heart, determination of urea clearance and the Addis test) were made on control and experimental periods. Visits were weekly or biweekly and measurements of urinary sodium were made from 24 hour urine specimens brought in at each visit.

2. *Results* (*Table 5*)

The most important difference between this and the inpatient group was the inadequacy of dietary control as measured from the urinary content in sodium. Only 3 patients (cases 2, 3, and 9) showed consistently low urine sodium contents at the level prescribed during the period of restriction, and another 2 reported with low urinary sodium contents regularly enough for us to calculate the effect of restriction in their cases. Control was not achieved in the remaining 8 patients; in only one of these (case 4) was there some association of arterial pressure level and urinary sodium content.

We are concerned only with the responses in the 5 patients who maintained their dietary control. Two of these responded to sodium restriction by decreased arterial pressure (cases 3 and 9).* One patient (case 12) showed a statistically significant decrease of systolic pressure during sodium restriction, but diastolic pressure was unchanged. Patients 3 and 9 indicated symptomatic improvement.

Discussion

Effect on Arterial Pressure

The hazards of evaluating effect of treatment of essential hypertension have been recently reviewed by Perera[18]; the Hippocratic dictum that the experiment is often fallacious and judgment always difficult applies with special force. The major criterion of a favorable response to sodium restriction in this study was a persistent decrease of arterial pressure to or toward normal levels and we have paid special attention to those patients in whom sequential periods of sodium restriction and repletion result in corresponding changes of arterial pressure. In view of the greater instability of arterial pressure in early essential hypertension, the patients selected for study suffered from severe established essential hypertension or from this condition in its malignant phase, and the severity of the disease in the group is shown by the fact that many died during or shortly after the periods of observation.

In using the criterion of decreased arterial pressure, a principal concern has been to obtain means during control and experimental periods which would be manifestly meaningful. We place no emphasis on pressure changes

* Case 3 in this series is responsive patient 9 of table 1.

which, while statistically significant, are clinically unimpressive. That the selection of means is adequate is shown (a) by the identity of pressure means in control and experimental periods in the nonresponders and (b) by the reproducibility of means under like conditions of sodium alimentation in responders. Some of the psychologic variables of dietotherapy were discounted by the use of enteric-coated tablets of sodium chloride, ammonium chloride and placebo during various phases of treatment with diets of constant composition. Consequently, we have every reason to believe that the responses of arterial pressure described above are due to sodium restriction as such and are in no way factitious.

Other Cardiovascular Responses

Fundal lesions of some patients regressed during treatment without changes in arterial pressure. These remissions may have resulted from rest and hospitalization. However, since relapses followed sodium re-alimentation in 2 patients, the remissions in these must be attributed to sodium restriction.

The cardiac status of the groups was, on the average, not unsatisfactory at the outset and did not change remarkably during sodium restriction, although marked improvement was seen in one patient.

Renal

(*a*) *Concentrating Power, Protein and Sediment.* These aspects of renal function were not greatly altered in most cases, although a favorable response was seen in one patient. The decrease of concentrating power during treatment with the rice diet is worthy of note, since it gives to the unwary the impression of a failure of this tubular function. The fact that administration of exogenous pituitrin restores this function to normal demonstrates that the apparent loss of concentrating power results merely from the fact that, in the absence of normal loads of urinary solids and electrolytes, a 24 hour period of water restriction is no longer an adequate stimulus to the hypothalamico-hypophyseal antidiuretic mechanisms. Lack of change of concentrating power in one patient on the rice diet indicates that in this case the output of urinary solids was being maintained, not from the diet, but from tissue catabolism; this ominous interpretation is consistent with the progressive wasting of this patient as the result of her unabated malignant hypertension.

(*b*). *Specific Renal Functions.* The functions of blood flow, glomerular filtration and tubular excretion tended in the group as a whole toward decreased levels. The depressions of function were more often attributable to the progress of hypertensive disease than to sodium or protein restriction, although 2 patients showed increased blood flow during protein feeding after treatment with the rice diet. The successive supplements of choline, methionine, Proteinum and Protolyzate given patient 14 were aimed at increasing the maximum tubular excretion of PAH from the level to which it had fallen during treatment with the rice diet. These were all ineffective and it may be that the decrease was due to progress of the disease during the lag period before improvement on dietary treatment. Thus, in perspective, our experience concerning renal function is in accord with that of Chasis, Goldring and associates.[14] However, just as we do not agree with them that sodium restriction is always ineffective in the treatment of hypertension, so we do not emphasize, nor have we demonstrated, a consistently deleterious effect of sodium restriction as such on specific renal functions.

(*c*) *The Low Salt Syndrome.* The azotemic and other deleterious effects of sodium deficiency (Schroeder[19]) as contrasted with the often beneficial effects of sodium restriction appeared during treatment in 2 patients. Both had at the outset suffered severe losses of renal function; it may be supposed that this had progressed to a point at which they were unable normally to retain sodium. Weakness and azotemia due to sodium deficiency were in both cases relieved by administration of 0.5 Gm. sodium daily as sodium chloride, while the beneficial effects of low sodium treatment were in both cases maintained.

The Rice Diet

Comparisons of this diet with the 0.2 Gm. sodium diet with Lonalac supplement were made in 6 patients. Four of these showed no response to either regime. One responded very favorably to rice, showed a severe increase of

arterial pressure and a recurrence of malignant hypertension with severe renal functional deterioration when sodium was incidentally administered during treatment with Protolyzate and thereafter failed to respond to the 0.2 Gm. diet. This seeming disparity of response is attributable to the very altered conditions under which the comparison was made in this case. One patient responded repeatedly to the rice and the 0.2 Gm. sodium diets in like fashion. These latter patients (figs. 3 and 4) vividly show the effect of addition of sodium to the rice diet in low sodium responders. In our experience, then, the antipressor effect of the rice diet is attributable to its low sodium content.

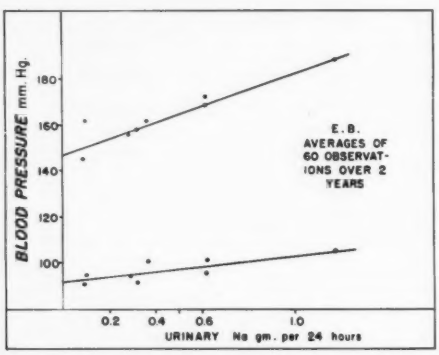

FIG. 1. Averages of observations on the relationship of arterial pressure and urinary sodium in patient 3 of table 5 (outpatient).

Kempner's claim that nitrogen balance could be maintained on the rice diet runs counter to current estimates of protein equilibrium. It is controverted in some degree by the experiments of Schwartz and Merlis[20] but has been recently confirmed by Peschel and Peschel.[21] Estimates were made in 2 of our patients by calculating the protein content of the food consumed on the rice diet and the nitrogen content of the urine (as "hypobromite-N," principally urea plus ammonia[22]) plus an allowance of 1 Gm. nitrogen daily for the fecal content. From this estimate patient 14 of table 2 was in about 1.3 Gm. daily positive balance after seven weeks on the rice diet. The stability of this body weight at this time is consistent with the estimate of approximate nitrogen balance. A more striking demonstration was made by similar methods in patient 13 of this series. After five weeks on the rice diet (period 10), she fractured her right femur. Estimates of nitrogen balance and also the urinary nitrogen: creatinine ratios were determined beginning on the third day after the accident. Figure 5 demonstrates the sequence of change. The nitrogen:creatinine ratio rose to a peak of 7 on the seventh day after the accident and then fell to a level of about 3 on the eleventh day. The levels of urinary nitrogen indicate that nitrogen balance, at first negative, became reestablished at about the same time. The changes in the nitrogen:creatinine ratio are interpreted as being the result of an initial breakdown of nonmuscle protein under the catabolic stress of the accident, with subsequent re-establishment of nitrogen balance at about the time expected in patients on diets of greater protein content. Thus, it not only seems possible to maintain and even to reestablish nitrogen balance while on the rice diet, but also to conserve a protein reserve.

Sodium Restriction: Level and Lag

The level of arterial pressure is, in an occasional patient, virtually a function of sodium intake (fig. 1). However, a review of the data indicates that significant responses usually occur only when the sodium restriction is such that urinary sodium is less than 0.5 Gm. per 24 hours and are most evident when the restriction is at the 0.2 Gm. level. The exception to this rule is the special case of the patient with "salt-losing" kidneys.

The lag of blood pressure rise and fall on restriction or refeeding of sodium is usually one or two weeks (figs. 2 and 3) although it may extend to four weeks (fig. 4). Thus, four weeks of sodium restriction at the 0.2 Gm. level of urinary sodium is necessary before a decision can be confidently made as to the patient's ability to respond favorably to such treatment.

Outpatient Treatment

Even among inpatients it is often difficult to maintain the desired sodium restriction. Medications, drinking water and other unsuspected sources of sodium abound. These possibilities of extradietary sources of sodium are multiplied in outpatients, in whom also the social, do-

mestic and psychologic difficulties of sodium restriction are greatly increased. For example, one outpatient found that her husband, dissatisfied with her remaining under medical supervision, deliberately salted all of her specially prepared food, including the gelatine dessert. Low sodium dietotherapy is therefore often impractical under the conditions of outpatient or office practice and demands at the very least a certain basic comprehension and compulsiveness on the part of the patient

Both among inpatients and outpatients, the

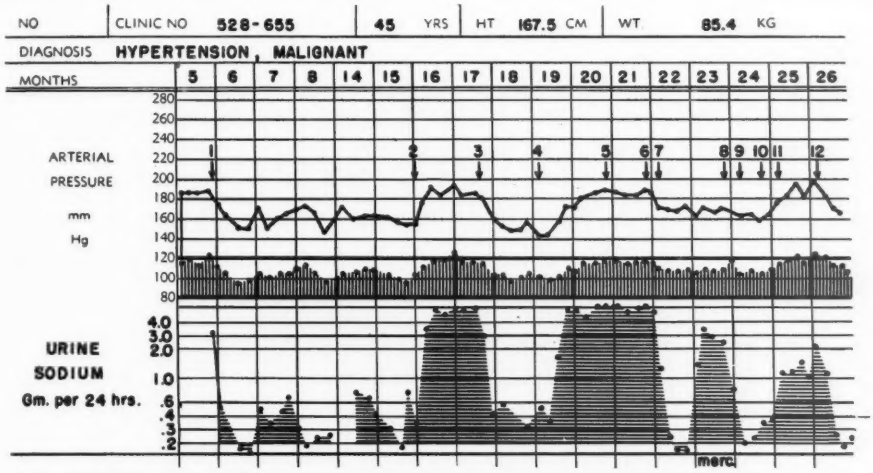

FIG. 2. Relation of arterial pressure and urinary sodium on Lonalac diet. Patient 12 (table 1). Periods charted are 1, on 0.2 Gm. sodium; 2, the same plus 18 Gm. sodium chloride; 3, the 0.2 Gm. diet only; 4, as in 2; 5, the same with ineffective ion-adsorbing resin; 6, as in 1 and 3; 7–12 reflect effects of varying dosages of sodium chloride and ion-adsorbing resins.

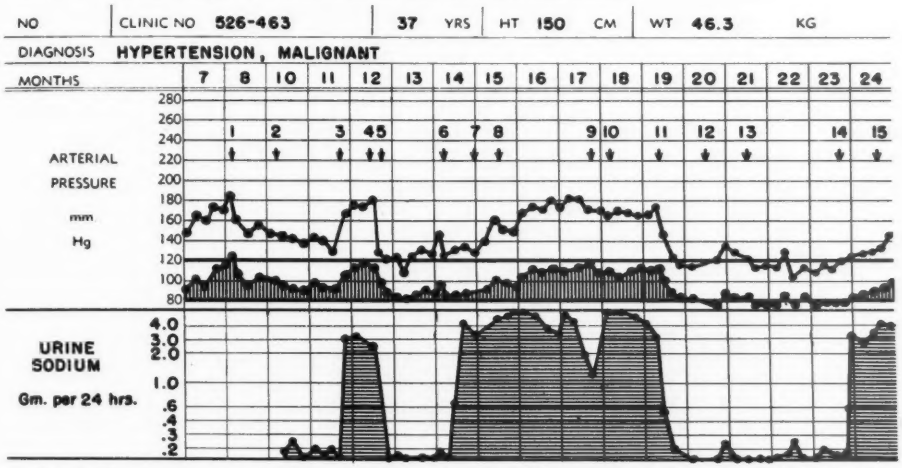

FIG. 3. Blood pressure and urinary sodium on rice diet with various supplements. Patient 13, table 1. Periods indicated are 1, pyrogenic extracts; 2, rice diet; 3, the same plus 8 Gm. sodium chloride; 4, rice diet; 5, 0.2 Gm. sodium diet; 6, ward diet; 7, 5.0 Gm. sodium diet plus 6 Gm. sodium chloride; 8, 0.2 Gm. sodium diet plus 18 Gm. sodium chloride; 9, 5 Gm. sodium diet plus 5 Gm. sodium chloride; 10, the same with 10 Gm. sodium chloride; 11, rice diet; 12, readmission with hip fracture; 13, 0.2 Gm. sodium diet; 14, 2.0 Gm. sodium diet plus 4 Gm. sodium chloride and 15, the same with 8 Gm. sodium chloride.

effect of sodium restriction can only be evaluated when the degree of restriction is indicated by frequent analysis of urinary sodium, and no opinion can be passed on the results of such treatment in their absence. Bryant[23] has recommended a simplified test for urinary chloride as a check on sodium restriction. However, his data suggest, and our experience has been, that at the low levels of urinary chloride found in patients on low sodium diets approximate chemical methods for chloride are not sufficiently sensitive. Further, the use by some patients of "salt substitutes" containing ammonium or potassium chloride, may vitiate the results of such analyses.

The besetting difficulty of treatment with low sodium diets is the unpalatability of the food. Some patients insist on the use of "salt-substitutes" which others find unpalatable; a fortunate few gradually lose the taste for salt and begin to appreciate the flavor of the food as such. But for many the dictum of Job (vi: 6–7) holds: "Can that which is unsavoury be eaten without salt, or is there any taste in the white of an egg? My soul refuseth to touch them; they are as loathsome meat to me."

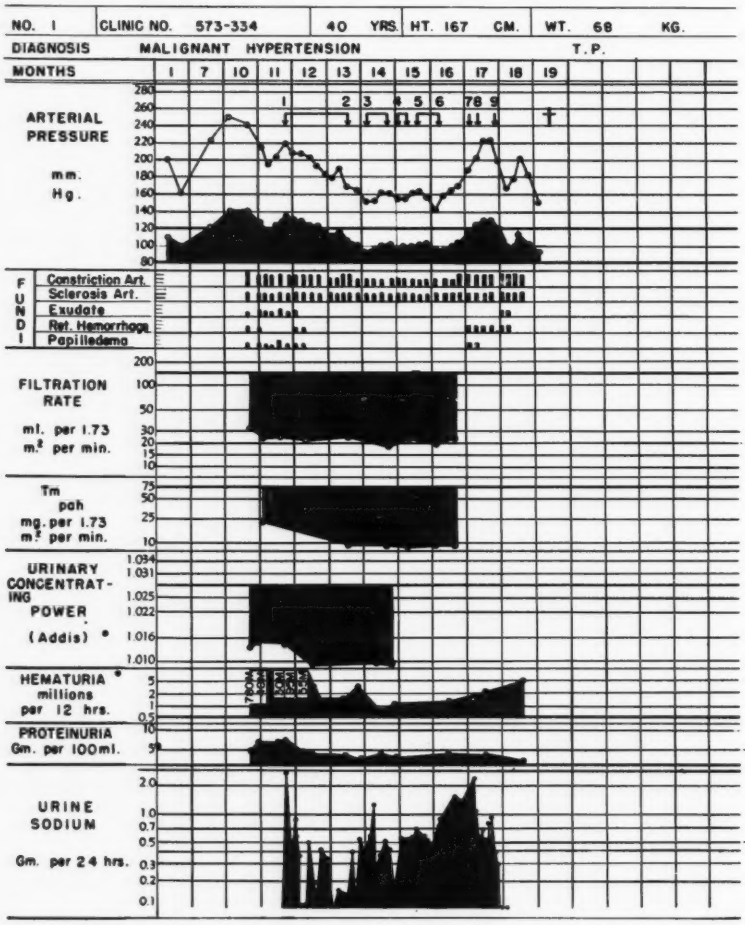

FIG. 4. Course of study in patient 14 on rice diet with supplements. Period 1 of the figure corresponds to periods 1 and 2 of table 1. Subsequent periods indicated in chart correspond to those of the table by adding one numeral, e.g., period 2 of the chart is period 3 of the table.

Mechanism of the Low-Sodium . . esponse

Observations made during this study on serum sodium, blood and plasma volume and the volume of distribution of thiocyanate show no association of changes in these to clinical responsiveness, and for this reason are not reported in detail. Current observations on sweat sodium concentrations on vascular responsiveness and total and fractionated urinary corticoids may yield a clue. Many facts point to a change in the function of the adrenal cortex or to a change in the response of vascular end

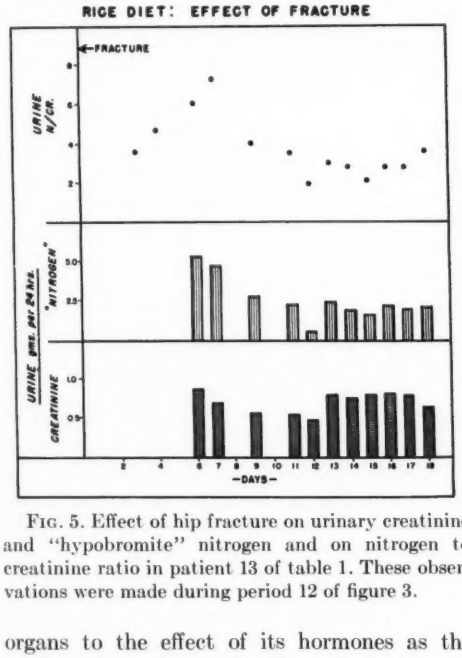

FIG. 5. Effect of hip fracture on urinary creatinine and "hypobromite" nitrogen and on nitrogen to creatinine ratio in patient 13 of table 1. These observations were made during period 12 of figure 3.

organs to the effect of its hormones as the primary determinant of sodium responsiveness. Of interest in this connection is the concept (Masson, Corcoran and Page[24]) that hypertension of nonadrenal origin may involve adrenal sodium-retaining and pressor hormones.

SUMMARY AND CONCLUSIONS

Roughly one-fourth of patients with severe essential hypertension act favorably to sodium restriction. The rice diet is in effect a practical low sodium diet, the hypotensive effect of which is dependent on sodium restriction. In the absence of azotemia it seems unlikely that the concurrent protein deprivation has an added beneficial effect, although on this diet it is possible to maintain nitrogen balance and even to conserve a protein pool. The minimum sodium restriction necessary for a response is about 0.5 Gm. sodium daily, with the exception of patients with "salt-losing" renal disease. This restriction must be maintained for four weeks for a conclusive test of responsiveness.

Although 4 of 14 outpatients responded favorably to sodium restriction, responses could only be maintained in two. Outpatient low sodium dietotherapy is at the least difficult and is often quite impractical. Our experience with the in- and outpatient series leads us quite categorically not to accept as valid observations on the effect of low sodium diets which are not secured by frequent determinations of urinary sodium output.

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Basic Hemodynamic Changes Produced by Aortic Coarctation of Different Degrees

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Basic hemodynamic studies on experimental coarctation of the aorta just beyond the left subclavian artery have revealed that hitherto unsuspected physical and physiologic factors are involved in creation of hypertension above a coarctation and in changes of pressure pulses below such a lesion. The effects are by no means explained by an increased resistance at the coarctation, as is generally believed. This communication analyzes the roles that changes in capacity and distensibility of the aortic compression chamber and increase in systolic discharge of the left ventricle play in the production of aortic hypertension, and discusses the physiologic compensations in blood flow by which an adequate return to the right heart is maintained despite extreme reduction in flow through the inferior cava. This communication also deals with the ways in which the pressure relations in the lower aorta and femoral artery are altered from the normal, emphasizing the relative shares that damping of the pulse wave and reduced input into the lower aorta play with different degrees of coarctation. The changing characteristics of the murmurs with progressive aortic constriction are also analyzed. The conclusion is reached that all the dynamic changes found in experimental and human coarctation are adequately explained without the assumption of accessory vasoconstriction through reflex or humoral agencies.

THERE IS general agreement that virtually all clinical cases of aortic coarctation manifest systolic hypertension above and systolic hypotension below the constriction.[1–3] The diastolic pressure in the cephalic vessels of the aorta is also generally elevated, though to a lesser extent, so that a large pulse pressure obtains. Differences of opinion exist as to whether the diastolic pressure in the femoral arteries is also raised. In 1928, Abbott,[1] in her statistical review of 200 autopsied cases, stated that the femoral diastolic pressure is changed but little. In 1937, King[2] reported cases in which diastolic pressures averaged more than those in normal subjects. Direct intra-arterial measurements of pressure in clinical cases of aortic coarctation have been reported more recently.[4–7] Although comparisons with indirect methods have not generally shown close agreement, they have indicated that systolic hypertension exists in the upper portion of the vascular bed and reduced systolic pressure in the lower portion. Again, great variability was found regarding femoral diastolic pressure. Thus, Brown and his associates,[6] using a hypodermic strain gage manometer, found that in 21 cases the femoral systolic pressure ranged from 87 to 133 (average 113) and the diastolic pressure from 63 to 99 mm. Hg (average 81). On the other hand, Bing and his associates[7] found in a series of 22 patients that, with one exception, diastolic femoral pressure was below normal. Such variability in diastolic pressure readings is not surprising, since the degree of constriction that exists in different patients naturally varies, and cases of different severity might have been fortuitously included in different groups of patients studied. Furthermore, it has been observed in this laboratory that needling of an exposed femoral artery of a dog can induce a reduction in the plethysmographic volume of a hind limb suggestive of vasoconstriction. Hence, it remains to be demonstrated that the maintenance or elevation of femoral diastolic

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pressure is not due to physiologic alterations incurred by the procedure used for determination of femoral pressure.

In the pressure pulses recorded from patients, chief attention has been focused on the arterial pressure levels; little attempt has been made to discuss the reasons for the alterations in pulse contours. In 1939, Woodbury and his associates published simultaneous intra-arterial pressure curves of the radial and femoral pulses in a case of coarctation. These indicated that the femoral pulse rises and falls much more slowly than the radial and that it is diminished in volume. The upstroke is delayed and slow, the peak broad, low, and rounded, and the contour during diastole is almost a smooth declining curve. Landmarks indicating the beginning of diastole are absent. Femoral pressure pulses exhibiting similar characteristics were published by Brown and his associates[6] and Bing and his group.[7]

These clinical observations have been supplemented by animal experiments, which, however, were designed chiefly to establish whether the hypertension above the coarctation can be explained as a physical result of the constriction. It has been amply demonstrated by means of acute experiments that the effects of complete aortic occlusion on mean pressure above the constriction depend on the level of compression. It is generally agreed that compression just above the renal arteries is without effect, whereas compression above the origin of the celiac axis[8] or above the diaphragm[9–12] causes an immediate rise of arterial pressure, as does compression of still more central regions. However, in chronic experiments it has been reported that constriction of the aorta just above the origin of the main renal arteries can also produce hypertension which is apparently not mechanical in origin.[13–17]

In 1940, Page[18] pointed out that occlusion of the aorta close to the site of origin of the renal vessels does not duplicate the dynamics of human coarctation, nor does it necessarily demonstrate that liberation of a renal factor is necessary for development of hypertension during aortic coarctation. Page discovered that, owing to development of collateral circuits, the aorta may be first partially and then completely constricted at the arch without development of hypertension proximal to the occlusion. On the other hand, he could produce hypertension of renal origin by constricting the aorta at the level of the diaphragm only when the aorta was also constricted a few centimeters below the origin of the renal vessels. In 1949, Harreveld restudied the subject in acute experiments. He found that the rise in arterial pressure produced by compressing the aorta above the celiac axis varies directly with the degree of stenosis and is roughly proportional to the diminution in blood flow through the constricted region. From this experimental evidence he concluded that the hypertension proximal to the coarctation is adequately explained by mechanical obstruction. Experimental compression of the aorta just beyond the aortic valves has also been studied to throw light on the dynamics of aortic stenosis.[19,20] Coarctation just beyond the left subclavian artery, which alone simulates clinical coarctation, has apparently been studied experimentally only by Page,[18] and surprisingly, the hemodynamic consequences have never been fully analyzed.

This investigation was, therefore, carried out to fill certain gaps in our knowledge by studying the arterial pressures and pulse contours in regions of the aorta above and below the stenosis. The effects that different degrees of constriction have on such pressure pulses, the reasons for changes in the femoral pulses that might be of prognostic value, and the determination of the extent to which physical factors alone suffice to explain the hypertension proximal to the constriction, all form part of this investigation.

Methods

Mongrel dogs were adequately anesthetized with sodium barbital, administered intravenously. Their chests were opened by a midsternal splitting procedure. Artificial respiration was instituted by means of an alternating air pressure and regulated so that natural lung inflation was simulated. The unavoidable loss of circulating fluid was compensated by giving a venous infusion of 100 to 200 cc. of warm, filtered, directly cross-matched, heparinized blood immediately after the major operation and by maintaining a slow drip during the experimental procedure. Aortic pressure was recorded by intro-

ducing a sound through the left subclavian artery so that its tip lay near the aortic valves. Femoral pressure was taken just below Poupart's ligament by means of a short cannula. In some experiments, abdominal aortic pressure was recorded by means of a small cannula via a renal artery. In other experiments, left ventricular pressure was registered by means of a blunt 15 gage needle introduced directly through the ventricular wall. In still other experiments, pressure pulses were also recorded immediately below the coarctation by inserting a glass T-cannula in the aorta. In these cases, in addition to the midsternal opening, the left side of the chest wall was separated sufficiently between the fourth and fifth ribs to give a satisfactory exposure of the posterior wall of the mediastinum. The upper 3 or 4 cm. of the descending aorta were freed from the posterior chest wall and the vertebral column, keeping close to the vessels so as to leave the thoracic duct undisturbed. The third and fourth intercostal arteries on both sides were then doubly ligated and divided. At this stage the animal was heparinized, and 0.5 cc. of heparin solution* was administered subsequently at 30 minute intervals. All cannulas were securely clamped to avoid vibrations.

Standardized Gregg-type optical manometers, with tensely stretched rubber membranes of adequate frequency and sensitivity, were used for the registration of all pressure pulses. Aortic constriction was produced by a special compressor, the construction and calibration of which has been described by Fineberg and Wiggers.[21]

One half to one hour was allowed, after the completion of the operative procedures, for stabilization of the circulation. The aortic compressor was then progressively tightened, records being obtained during successive steps of the compression. Following each record a short calibration of optical manometers was made with a fixed standard pressure. The zero pressure in all experiments was taken as the hydrostatic level of the animal board, hence pressures as measured were 15 mm. Hg higher than the actual pressures. A complete calibration of each manometer was carried out at the end of each experiment. After the experiment had been completed the loop of cord around the aorta was left in its original position, the aorta was cut without disturbing the cord and its internal diameter was measured, as previously described.[21] The degree of stenosis in terms of the percentage of the normal was calculated from the reduction in the area of the aortic lumen with progressive degrees of coarctation.

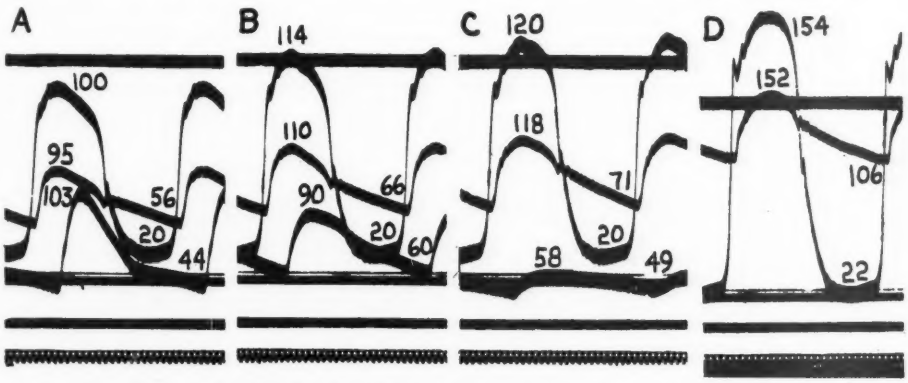

FIG. 1. Pressure pulses showing the effects of progressive coarctation of the aorta on the central aortic, femoral and left ventricular pressure curves. Upper curve, ventricular pressure; the middle one intersecting the ventricular, central aortic pressure; lower curve, femoral pressure. Segment *A*, control unconstricted aorta; segments *B*, *C*, and *D*, effects of 61, 85 and 95 per cent reduction in the aortic lumen. In the interval between taking records *C* and *D* the ventricular manometer mirror and base line mirror were shifted, without altering the relation between the two, to allow the entire ventricular pressure curve to be recorded.

RESULTS

The segments of figure 1 show the effects of progressive coarctation of the aorta on the central aortic, femoral, and left ventricular pressure curves. It will be seen that, as the degree of coarctation is increased, both systolic and diastolic pressures rise in the central aorta and that the amplitude of the curves, i.e., the pulse pressure, increases. Contrariwise, the

* The heparin solution used in these experiments was supplied in part by The Upjohn Company, Kalamazoo, Mich.

femoral pressure pulses show a progressive reduction in systolic, diastolic and pulse pressures until a stabilized mean pressure of 22 mm. Hg is reached in segment *D*.

The average trend of aortic and femoral pressures in 22 dogs with different degrees of aortic constriction is shown graphically in figure 2. The following deductions are self-evident: (1) A reduction of more than 45 to 55 per cent in the aortic lumen is required before the arterial pressures in the aorta or femoral artery are affected. With a 55 to 65 per cent stenosis, the average aortic diastolic pressures are approximately the same and the average aortic systolic pressure has increased only slightly. At the same time, the average femoral systolic pressure declines to a greater degree. (2) With progressive increase in coarctation, there is an accelerating increase in the systolic pressures above the stenosis, but the average diastolic pressure does not change until the aortic lumen is reduced to more than 65 per cent of its original size. It then shows a rise much smaller than systolic pressure. Thus, there is a progressive increase in the pulse pressure above the coarctation. The maximum increase in systolic and diastolic pressures does not supervene until the aortic lumen has been reduced to about 90 per cent. With progressive reduction of the aortic lumen beyond 55 to 65 per cent, the fall in femoral systolic pressure is greatly accelerated. The diastolic pressure also falls, but not to the same extent. Thus, the pulse pressure keeps on decreasing, and at about 85 to 95 per cent stenosis it becomes so small that a femoral pulse is just discernible. This is quite understandable, for when the aorta has a larger lumen a certain percentile

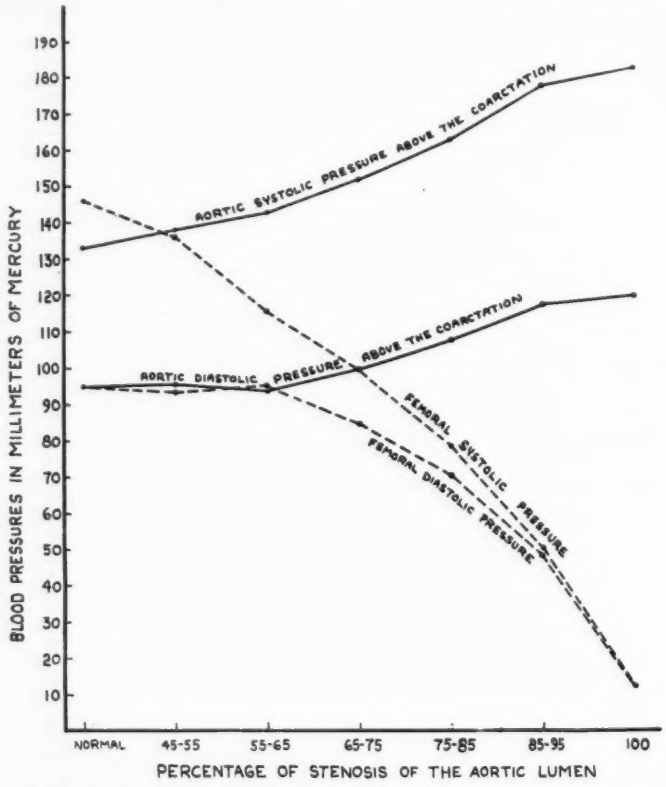

FIG. 2. Chart summarizing average aortic and femoral systolic and diastolic pressure changes with progressive coarctation of the aorta.

decrease alters its area proportionately much less than the same percentile decrease does when the lumen is narrow. Neglecting any change in pressure, the volume of blood flowing through a stenosed lumen varies as a fourth power of the radius of the aorta at that level and, according to Poiseuille's law, the flow should be suddenly curtailed to a greater extent in extreme degrees of coarctation.

Effect of Progressive Aortic Compression on Aortic Pressure Contours

In order to interpret the effects of progressive narrowing of the aorta on the pulse contours beyond a constriction it is important to know how the parent pulses central to it are modified. This has so far not been accomplished by studies of human subjects.

An analysis of many records revealed that changes in the configuration of the central aortic pressure pulse depend not only on the degree of constriction but also, to a considerable extent, on the stroke volume and competence of the left ventricle. This is illustrated by aortic pressure pulses in figures 1, 3, 4 and 5. Figure 1 indicates that the systolic discharge previous to compression (segment *A*) was obviously below par. Consequently, progressive aortic compression merely serves to restore the aortic contours to forms that resemble those recorded from normal dogs and human subjects. This process was accompanied by changes in intraventricular pressure typical of increased aortic resistance. Figure 1*A* shows that the amplitude of the curves progressively increases, the isometric gradients become steeper, and the peaks are displaced progressively toward the end of systole; but in this case a measurable increase in initial tension and in duration of systole occurs only in segment *D*, i.e., after complete occlusion of the aorta. Apparently, the left ventricle is capable of compensating fully in such instances; indeed, judgments based on the increasing pulse pressure and forms of the aortic pulses strongly indicate that the systolic discharge is increased. This is supported by values obtained in several experiments through application of the Hamilton-Remington technic.[22,23] The data from one of these analyses are concisely incorporated in table 1, which, incidentally, reveals that the calculated total peripheral resistance expressed in absolute units (A.U.) is not significantly raised until constriction equals 70 per cent of the natural aortic diameter.*

Figure 3 illustrates records from an experiment in which the control aortic pressure pulse has a contour which is essentially normal for dogs and man, although the diastolic and systolic pressures are a trifle high. With increasing aortic compression, as exhibited by successive segments, the top of the pressure curves assumes more and more an ascending plateau, terminating nearer and nearer the end of systole. These are characteristic effects, commonly described as due to increasing peripheral resistance.

TABLE 1.—*Effect of Progressive Coarctation on Mean Aortic Pressure, Stroke Volume, Cardiac Output, and Total Peripheral Resistance.*

Degree of Stenosis as Per Cent of Normal	Heart Rate per Minute	Mean Aortic Pressure	Stroke Volume	Cardiac Output	Total Peripheral Resistance Large A.U.
		mm. Hg	*cc.*	*cc.*	
Normal	183	142	126	2305	4.926
60	173	146	137	2361	4.95
65	173	162	149	2566	4.866
70	167	174	160	2662	5.226
75	163	174	156	2660	5.148
83	164	179	147	2420	5.928
95	159	180	159	2521	5.73

Figure 4 shows records from an animal in which hypertension existed before compression began. It shows that the systolic pressure is not necessarily elevated further in such instances through progressive constriction of the

*It has been our experience that calculations of systolic discharge and cardiac output by the pulse contour method[22,23] are at times consistent and at other times inconsistent with expected or otherwise determined values during changing hemodynamic states. The augmentation of cardiac output as a result of aortic compression indicated in table 1 corresponds, at least directionally, with results in similar experiments in which cardiac output was determined from cardiometer records. It is interesting to note that this was true despite the fact that the basic premises upon which the procedure was founded were probably disturbed through high constriction of the aorta (C.J.W.).

aorta. Indeed, an actual decline may take place. There is, furthermore, a considerable fall of diastolic pressure which is chiefly responsible for the larger pulse pressure. The pressure pulses, instead of tending toward a rising systolic plateau, decline during the latter portion of systolic ejection. Such transformations are attributable to an altered pattern of

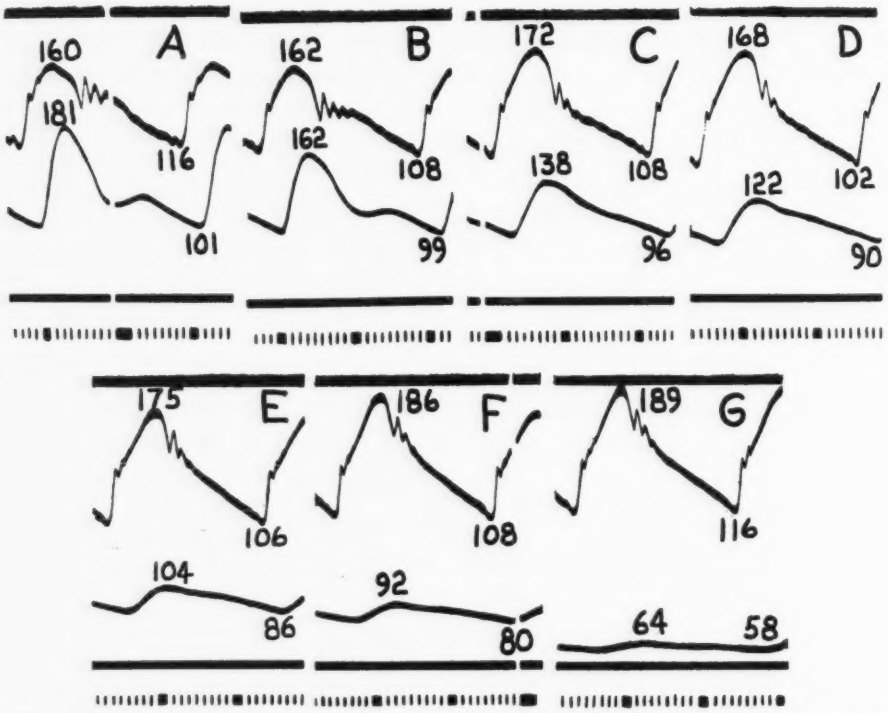

FIG. 3. Effects of progressive coarctation on the aortic (upper curves) and femoral pressure pulses (lower curves). Segment *A*, normal relationship between the central aortic and femoral pulses. Segments *B*, *C*, *D*, *E*, *F* and *G* show effects of 60, 65, 71, 76, 80 and 85 per cent reduction in aortic area at region of the constriction.

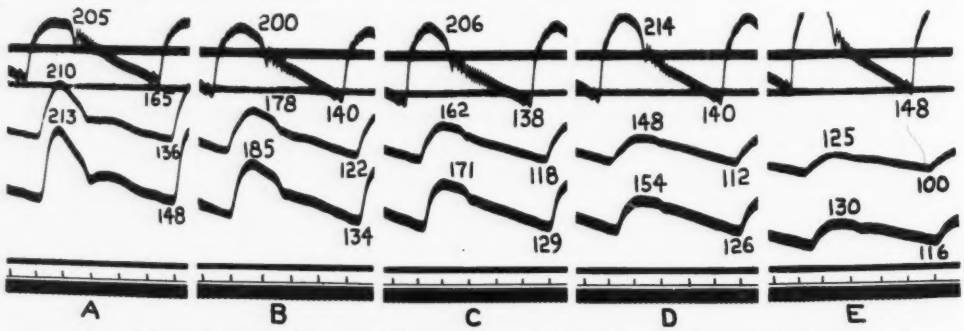

FIG. 4. Effects of progressive coarctation on the central aortic (upper curve), abdominal aortic (middle curve) and femoral arterial (lower curve) pulse contours. Segment *A*, normal relationships when the aorta is unconstricted; segments *B*, *C*, *D* and *E*, effects of 54, 64, 78 and 83 per cent reduction in the aortic lumen.

systolic ejection, the ventricles apparently emptying a larger fraction of their systolic stroke volume during the early moments of ejection.

Figure 5 shows the changes in central aortic pressures during an experiment in which a glass cannula had been inserted into the aorta. The curve is much more peaked, owing to a marked decline of pressure toward the incisura during late systole. Such a late systolic collapse indicates a disproportion between aortic uptake and efflux, due either to reduction in resistance or in ventricular discharge during the period under consideration. The possibility

Effect of Different Degrees of Aortic Compression on Contours of Femoral Pressure Pulses

The progressive changes in femoral pulses are also shown in figures 1, 3, 5. The curves exhibit a progressive reduction in amplitude and a retardation of the anacrotic limb. The summit appears increasingly later in systole and, instead of being sharp and peaked, is broad and rounded. A more careful study of such records suggests that the transformation occurs in two stages: (1) With moderate constriction the femoral systolic pressure no longer exceeds aortic pressure, as is normally the case; it

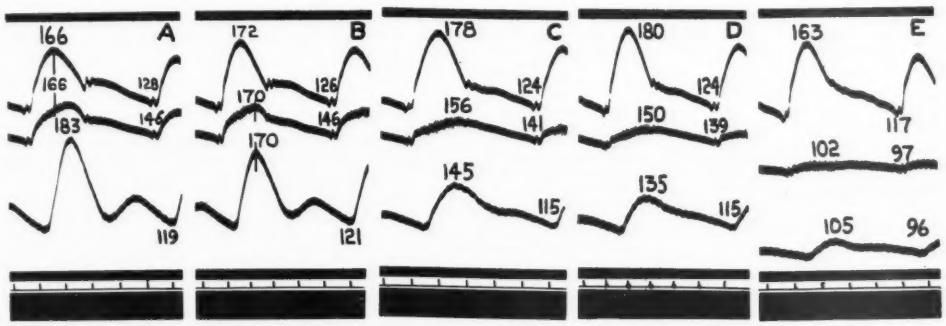

FIG. 5. Effects of progressive aortic coarctation on the contour of the aortic, femoral and thoracic pressure curves. Upper curves, pressure in aortic arch; middle curves, pressure pulses from the thoracic aorta immediately below the coarctation; lower curves, femoral arterial pressure pulses. Segment *A*, control with unconstricted aorta; segments *B*, *C*, *D* and *E*, changes during 55, 65, 75 and 85 per cent stenosis.

that the peak is deformed through reflected waves has been considered and discarded. That the altered form of central aortic pressure pulse is due to an abnormal pattern of ventricular ejection in this experiment is supported by the facts that (1) the collapsing characteristic is maintained even when pronounced constriction of the aorta has occurred (segments *B*, *C* and *D*), and that (2) in similar experiments the normal configuration was preserved.

The foregoing illustrations emphasize the importance of being familiar with the configuration of central aortic pressure pulses possible in experimental animals and in clinical cases, for they determine largely the effect of progressive coarctation on pressures above the lesion and on contours of pulses below it.

either equals it, as in figure 3*B*, or is less, as in figure 5*B*. Also, the contour of the femoral pulses is but slightly affected. (2) With further constriction, illustrated by subsequent segments of these figures, the dicrotic wave becomes less and less prominent and is finally abolished, the landmarks separating systole and diastole disappear, and the diastolic decline of pressure becomes essentially a smooth curve. At the same time, the pulse pressure diminishes progressively through a predominant fall in systolic pressure. The peak of the pulse is also conspicuously—and palpably—retarded, e.g., from 0.128 second in segment *A* to 0.2 second in segment *G* of figure 3, but an anacrotic halt characteristic of stenosis at the aortic valves is absent in the curves. The pulse wave is also delayed in its transmission, but

not conspicuously so. For example, the lag increased only from 0.056 second in segment *A* to 0.074 second in segment *G* of figure 3.

pulses were recorded in some experiments from the descending aorta at the level of the renal artery and immediately below the coarctation.

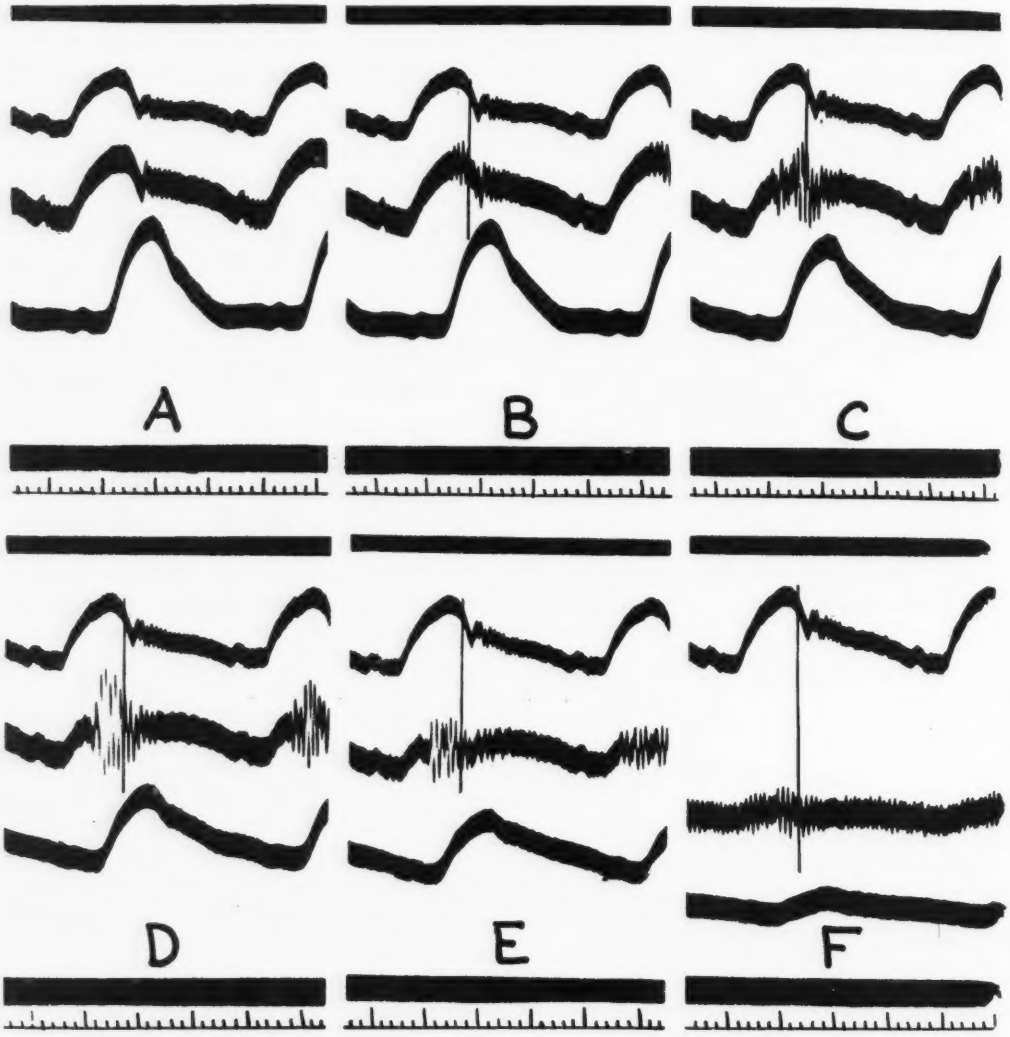

FIG. 6. Records showing the murmurs produced by coarctation of the aorta. Upper curves, aortic pressures above coarctation; middle curves, aortic pressures immediately below coarctation; lower curves, femoral pressures. Segment *A*, control with unconstricted aorta; segments *B*, *C*, *D*, *E*, and *F*, effects of 60, 68, 73, 78 and 86 per cent stenosis.

Effect of Progressive Compression on Pressure Pulses beyond a Constriction

In order to interpret the changes in femoral pulse contours more satisfactorily, pressure

In experiments in which the central aortic pressure pulses resembled those shown in figures 1, 3 and 5, the aortic pressure pulses recorded via a renal artery resembled those in

the femoral artery as regards main characteristics. This indicates that the transformation has taken place by the time the pulse wave reaches the lower aorta. The curves of figure 4 are introduced to illustrate that the basic transformation of the peripheral pulses is not altered by progressive coarctation when a state of hypertension exists before the compression. The middle record of this figure shows that the pressure pulses from the lower descending aorta resemble those taken from the femoral artery (lower curve). It may be noted that, as previously described by one of us in cases of human hypertension,[24] the incisura of the central pulse is well transmitted to the periphery, even when the aorta has been constricted to 64 per cent of its original size (segment *C*).

Returning to figure 5, the middle curve portrays pressure changes in the aorta just distal to the coarctation. Crosslines drawn in segment *A* show that at the time the peak of pressure is reached above the constriction (upper curve) the pressure is the same below the constriction (middle curve). However, the pressure continues to rise below the constriction while it declines above it. Since the summit practically coincides with the peak of the femoral pulse, it follows logically that a standing wave is added to the pressure curve in this region. This interpretation becomes more plausible by a glance at segment *B* of figure 5, in which a definite wave is superimposed after the aorta has been slightly constricted. With increasing degrees of compression, the initial steep rise becomes less and less and the curve continues as a protracted rise until the incisura. Fine vibrations, irregular in size and frequency, can also be observed on the rising pressure curve. These occasionally extend even beyond the incisura, which becomes progressively less conspicuous. The pressure oscillations are graphic representations of the systolic murmur that accompanies coarctation. It will be observed that these murmur vibrations do not start from the anacrotic halt of the pressure pulse but are separated from it by a short period of smoothly rising pressure. Since there is no similarity between these curves and those taken from the femoral artery, it is obvious that the transformations that occur in the femoral pulse with increasing degrees of constriction do not arise immediately below the coarctation.

Figure 6 is an original record of the murmurs in progressive coarctation of the aorta. Normally, in segment *A* the curve recorded from the glass cannula is free of any murmur. As the stenosis is increased to 60 per cent (segment *B*), a late systolic crescendo murmur of short duration appears. With 68 per cent reduction of the aortic lumen (segment *C*), the systolic murmur starts about the middle of the ascending limb, is still crescendo, and is continued as a diastolic decrescendo murmur. On increasing the coarctation to 73 per cent (segment *D*), a crescendo-decrescendo murmur reaching great intensity starts about one-third up the ascending limb. The decrescendo portion continues into early diastole. With still further increase in coarctation to 78 per cent (segment *E*), the murmur becomes less intense. In severe degrees of coarctation (segment *F*), the murmur is present throughout systole and diastole, but its amplitude becomes so small that it is no longer audible. The vibration frequency of the murmur varies between 120 and 138 per second.

Discussion

Similarities of Clinical and Experimental Coarctation. Femoral pressure pulses, recorded from patients with aortic coarctation by Woodbury, Brown, Bing, and their respective associates,[5–7] are very similar to those that we produced by experimental coarctation. The results of our experiments are, therefore, applicable to clinical cases of coarctation. However, in patients, equivalent degrees of aortic constriction may not affect the femoral pressure pulses to the same extent, owing to established collateral channels. (See succeeding article.)

It is common clinical knowledge that a palpable delay exists between the radial and femoral pulses in patients with marked aortic coarctation. Measurement of our records, however, reveals that the increased delay in transmission of the pulse wave from the aorta to the femoral artery is too small to be detectable by palpation. Since the tactile stimulus is given by the primary rise of pulse waves,

the difference in their summits, which is significantly greater owing to the slow rise of the femoral pulse, probably accounts for the clinical impression of a delay. Somewhat similar interpretations were made by Lewis[25] and Feil and Gilder[26] in other disorders.

The slow rise of the femoral pulse, evident in experimental and clinical pressure pulses, may be appreciated by palpation. It is due in part to the damping of the parent wave at the constriction and in part to the failure of a less forceful impact to set up a standing wave in the aorta, thus preventing summation of pressure on the anacrotic limb and a systolic overshooting, such as occurs in the normal femoral pulse.[27] (For further discussion, see later part of paper.)

Hemodynamic Alterations above the Coarctation. The physiologic and physical effects cephalad to the region of coarctation are not limited to those produced by increased resistance alone, as is commonly inferred. They involve also changed characteristics of the aortic compression chamber, adaptations of the left ventricle, and adjustments of flow which assure an adequate venous return.

Our data reveal that the resistance effects exerted by progressive narrowing of the aorta are detected sooner through elevation of left ventricular and aortic systolic pressures than in calculations of total peripheral resistance (TPR). For example, as shown in table 1, a 60 to 65 per cent constriction is without significant effect on TPR, but causes a significant change in left ventricular pressures (fig. 1*B*). When central arterial pressures are greatly elevated, as in figure 4, the larger pulse pressure may be due, in part at least, to the rapidly diminishing distensibility of the aorta, but this does not explain the increase at lower pressure ranges, such as persist in the curves of figure 1*C*. The suspicion that systolic discharge is also increased is supported by calculations shown in table 1. This increase in systolic discharge is an important factor in the larger pulse pressure when the left ventricle compensates. When such compensation does not occur systolic pressure may even decline slightly, as in figure 4. In these cases the increase in pulse pressure is due entirely to reduction of diastolic pressure, the cause of which may now be discussed.

Lowering of resistance through opening of natural collateral channels can be excluded in these experiments, for the decline of diastolic pressure occurs too promptly and is not prevented by ligation of all accessible large collaterals. The temptation at once arises to invoke reduction of resistance in aortic branches above the coarctation through aortic and carotid sinus reflexes. In addition, it has been found in similar experiments performed in this laboratory that resistance to coronary flow decreases, partly for mechanical reasons[28] and partly through local actions of metabolites.[29] As a result, the coronary channels carry a large fraction of the flow that is prevented from leaving the aorta through a stenotic orifice. Incidentally, this insures a better blood supply for the hyperactive ventricles. However, the concept that the decline of diastolic pressure is due to reduced resistance in branches of the aortic arch is inconsistent with (1) the absence of changes in heart rate such as generally occur pari passu with reflex vasomotor changes when pressoreceptors in the aorta and carotid sinus are excited by a rise in arterial pressure; (2) the failure of calculations (table 1) to indicate that a reduction in TPR has occurred; and (3) the maintenance rather than decline of diastolic pressure below the stenosis. If reflex dilatation of arterioles had taken place, those in the splanchnic area, kidneys, and hind limbs would have been affected to an even greater extent and, hence, diastolic presure below the stenosis would have declined. Obviously, some factor other than reduction in resistance in aortic branches must be responsible for the total changes in central pressure pulses, viz., the rise of systolic and decline of diastolic pressures, and the slight increases in systolic discharge and calculated total peripheral resistance while the heart rate remains constant (figs. 3, 5).

Dynamic studies on artificial circulation machines (Wiggers[32]) show that such a com-

bination of changes does result when the distensibility of the compression chamber is reduced. Upon reflection, this is the situation that develops during aortic coarctation: the compression chamber is greatly reduced in size and its walls are put under greater stretch. Hence, we attribute the effects on systolic pressure (in part) and on diastolic pressure (entirely) to an increase in the volume elasticity coefficient $\left(\frac{dp}{dv}\right)$.

We have referred to the possibility that systolic discharge and cardiac output may be augmented as a reaction to aortic compression. Since this occurs with compression of 55 per cent or more, and despite the fact that aortic pressures below the constriction have declined to low levels, it would seem that the venous return via the inferior cava must be drastically reduced. Since augmented cardiac output can be maintained only when the total return flow is adequate, the inference follows that the reduced inferior cava flow is compensated by increased flow through the superior cava and coronary venous system. That this is true has been demonstrated by Katz and Wiggers,[33] who found in similar experiments that right arterial and ventricular pressures may even be slightly elevated and that this is not due to "back pressure effects." As inferred by these authors, the greatly augmented flow through the coronary system contributes greatly to rebalancing the venous return.

Hemodynamic Alterations below the Coarctation. In order to interpret changes in pressures and pulse contours below aortic coarctation of various degrees, the dynamics of pressure transmission in the aorta under normal circumstances must be kept in mind. The transformation that the aortic pressure pulses undergo during their passage through the aorta has been discussed by several recent writers.[30–32] The changes are chiefly caused by natural damping in a low frequency system and superposition of standing waves. Under normal conditions, natural damping results in (a) a retardation of the rise of the initial part of the pressure pulse, (b) some rounding of the summit, and (c) annulment of finer oscillations such as the pre-ejection vibrations and sharp incisura and its after-vibrations. The superposition of a standing wave causes the pressure wave in the lower aorta (a) to rise rapidly to a higher pressure peak than exists in the ascending aorta, (b) to decline rapidly during late systole and early diastole, and (c) to develop a dicrotic dip succeeded by a dicrotic wave of considerable size. These changes are transmitted to the femoral arteries (cf. figs. 3*A*; 5*A*.) These natural transformations can be modified decidedly by changes in (a) the elasticity coefficient of the aorta, (b) peripheral resistance, (c) other conditions that alter the natural frequency of the aortic reservoir and rate of travel of reflected waves and, as in these experiments, (d) damping of the parent pressure waves at the constriction. A great deal concerning this last factor can be learned by progressive damping of an optical manometer through gradual closing of a stopcock while aortic pressure pulses are being recorded. A large experience with such trials has helped us to interpret the effects of progressive degrees of coarctation on the femoral pressure pulses. But the effects are not quite identical, for a great deal depends upon the natural frequency of the system which picks up the damped vibrations. The inherent frequency of the descending aorta is very low, usually 3.6 to 5 per second. It increases when the walls are stretched, as in hypertension; it decreases when the walls become more lax during hypertension, as in these experiments.

Under circulatory conditions that develop with progressive aortic compression, damping reduces the force of the initial impact as blood is ejected. Consequently, as soon as this is not sufficiently violent to set the aortic blood column into oscillation no standing wave is induced.[20] The effect of critical damping appears early during compression, so that with approximately 55 per cent compression systolic pressure in the femoral artery becomes equal to or slightly less than that in the aorta, but, owing to the low frequency of the arterial system, the pulse contour is deformed. After

greater degrees of stenosis, the systolic and pulse pressures progressively decline and the ascent becomes more gradual. However, the delay in transmission is not conspicuously affected.

The effects simulate progressive damping of mercury manometers used for arterial pressure recording. As in these, so in the aorta, progressive damping decreases the amplitude of oscillations until only a mean pressure is transmitted. Since the configuration of pressure waves places the mean nearer to the diastolic pressure, it follows that diastolic pressure is sustained relatively better than systolic. In this way, the relatively high diastolic pressure is explainable without invoking the operation of arteriolar vasoconstriction and liberation of a humoral agent to activate such a process. Parenthetically, it is our considered opinion that, while it is quite possible, in chronic coarctation, that a renal factor may contribute to the hypertension above a stenosis and to the sustenance of diastolic pressure below, the latter cannot be used as evidence for the existence of increased resistance. Likewise, studies of blood flow in the lower extremities of patients with coarctation are incapable of determining the existence of increased arteriolar constriction, for it is not known what the pressure-flow relations would be at equivalent pressures under normal conditions.

Concerning Turbulence. It has long been suspected, from a priori physical considerations and the presence of a murmur, that a state of turbulence is created beyond an aortic constriction. Our records reveal that they resemble vibrations previously reported in aortic valvular stenosis.[19,20] In some cases (fig. 6) the murmur is preceded by a sharp incisura, but this is not followed by an anacrotic femoral pulse, indicating, as Dow[20] found, that the two are not related as cause and effect phenomena.

We have seen no evidence that such a local turbulence beyond the stenosis has any effect on the pulse contours in the lower aorta and femoral artery. However, a few interesting features were noted: (1) The murmur appears before pressure relations are significantly affected (fig. 6*B*); hence, greater importance should perhaps be placed on auscultatory phenomena in suspicious diagnosis of incipient states of coarctation. (2) The murmur increases in intensity up to a degree of stenosis critical for pressures cephalad to the constriction, and thereafter diminishes (fig. 6*D*, *E*). The magnitude of constriction can, therefore, not be judged from the intensity of murmurs heard on auscultation. (3) The murmur starts after ejection and extends into the early phase of succeeding diastole, i.e., as long as a considerable pressure gradient for maintaining the turbulence continues.

The question has, naturally, been considered whether the development of turbulence, like the erosive action of a whirlpool on stream banks, may not have some deteriorating effect on the vascular walls, causing them to weaken or lose elasticity, thus creating a hemodynamic factor which is responsible for the subsequent dilatation below the stenosis. Such a suggestive explanation must be held sub judice until we have more basic information regarding the effects of turbulence on stream boundaries of fluids contained in tubes.

Summary

1. The basic hemodynamic factors that determine pressure relations above and below an aortic coarctation were studied experimentally in dogs by recording pressure pulses from the aortic arch and femoral artery, and also, in certain experiments, from the left ventricle and different levels of the descending aorta, by means of calibrated optical manometers.

2. Various degrees of circular constriction up to complete occlusion were produced in the aorta just beyond its left subclavian branch by means of a special compressor that could be calibrated at the end of an experiment.

3. Measurements of calibrated pressure curves revealed that a reduction in aortic lumen greater than 45 to 55 per cent is required to produce any changes in arterial pressures. The effects of successively greater reductions on systolic, diastolic, and pulse pressures above

and below the constriction are conveniently summarized in figure 2.

4. In order to evaluate the pressure changes beyond an aortic coarctation one must be familiar with the configuration of the parent aortic pressure pulses above the stenosis. Since these alterations have apparently not been taken into account in previous hemodynamic analyses of aortic coarctation, modifications of the aortic pressure pulses, induced by varying degrees of constriction, were first carefully analyzed.

5. Such studies revealed that the hypertension in the aorta above a coarctation is not due solely to increased resistance, as has been commonly inferred. Equally important are (a) the reduced capacity and distensibility of the aortic compression chamber into which the left ventricle empties its blood during each systole and (b) the physiologic reactions of the left ventricle whereby its systolic discharge is increased. The latter were interpreted by analyses of left ventricular pressure curves.

6. Since the venous return to the heart by way of the inferior vena cava must decrease progressively as the degree of aortic constriction increases, it would obviously be impossible for the left ventricle to maintain a larger cardiac output unless compensatory increases in flow took place through various branches of the aortic arch, including the coronary system. Previous evidence from this department that such compensatory flow takes place was substantiated. It is evident that any mechanism which reduces the flow through branches of the aortic arch, such as the reflex or humoral constriction of arterioles, would not be a propitious event, and we have discovered no evidence that such reactions supervene.

7. The corollary follows that augmented resistance in small terminals of the aorta proximal to a coarctation can probably contribute little to the hypertension of aortic coarctation. By reducing blood flow through these circuits, the venous return to the heart would be so seriously impaired that cardiac output of the left ventricle would be reduced and aortic pressures would automatically decline. In short, the hypothesis that the hypertension of aortic coarctation is due to a renal factor is difficult to square with dynamic laws.

8. Studies of pressure pulses in the descending aorta at various distances beyond the stenosis indicate clearly that the changes in configuration of the femoral pulse start above the level of the renal arteries. The slow gradients of the anacrotic and catacrotic limbs and the abrogation of the dicrotic wave and notch, which characterize femoral pulses in severe coarctation, are the direct result of damping of the aortic pressure wave in its passage through the constriction. Since the impact imparted to the blood column by the force of ventricular systole is reduced, the aortic blood column is not thrown into oscillation and the normal standing wave is not created. In consequence of the latter, the gradient of pressure rise decreases, the normal systolic overshoot is prevented, and the dicrotic wave is abrogated. The damping factor is also the important factor that causes a smaller pulse amplitude during moderate degrees of aortic constriction, but the diminishing pulse volume that reaches the descending aorta is obviously of dominant importance in more severe grades of stenosis.

9. To a considerable extent the relatively good maintenance of femoral diastolic pressure as systolic pressure falls is also an indirect effect of damping. Damping tends to reduce pressure variations toward a mean level, such as is actually realized in very severe stenosis. With lesser degrees of stenosis and damping, pulse pressures merely diminish, but since the mean pressure lies nearer to the diastolic level the latter pressure is better maintained than is systolic pressure. The corollary follows that a comparatively high femoral diastolic pressure is not dynamic evidence that additional vasoconstriction exists in branches of the lower aorta.

10. With progressive aortic constriction, a murmur indicating a state of turbulence just beyond the constriction begins to appear before pressure relations are significantly altered above and below a constriction. The intensity of the murmur first increases and then de-

creases with progressively greater constriction. It begins shortly after the pressure rise and extends slightly into diastole, i.e., it continues as long as a pressure gradient exists across the constricted region. The question whether the turbulence created below the coarctation develops forces which may weaken the arterial wall and subsequently lead to dilatation of the aorta cannot be answered until we have more information regarding the effects of turbulence on stream boundaries of fluids in elastic tubes.

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The Effects of Arterial and Pulmonary Shunts on the Dynamics of Aortic Coarctation

By TRILOK CHAND GUPTA, M.D., PH.D.

This communication deals with the manner in which collateral arterial channels and a persistent ductus arteriosus affect the dynamics of an uncomplicated aortic coarctation which was studied experimentally by means of artificial shunts and registration of pressure pulses. The conclusion is reached that effective collaterals or a surgical subclavian-aortic shunt can be effective dynamically in reducing hypertension and left ventricular strain and in providing an adequate flow through tissues despite the fact that the femoral pressure pulse does not revert to a normal form. The presence of an aortic-pulmonary shunt affects aortic pressure both through reduction in aortic resistance and augmentation of systolic discharge until very severe degrees of coarctation exist. The right ventricle of the normal heart can function as a systemic ventricle only when the aorta is almost completely occluded.

THE BASIC dynamics of aortic coarctation were analyzed in the preceding communication.[1] In man, however, coarctation of the aorta is always complicated by the gradual development of numerous anastomoses which provide sufficient blood flow to the lower aortic branches to maintain life processes reasonably well. Nature's experiments, therefore, differ from acute experiments in that patients manifest hypertension above the constriction despite the development of such collaterals. The question, therefore, arises as to whether the resistance of the cephalic aorta and its branches is still high or whether additional constriction of the peripheral arterioles is involved. The purpose of this investigation was to simulate naturally developing collaterals by making a functional shunt between a subclavian artery and the aorta, and to study the hemodynamic effects of opening and closing such a shunt. Incidentally, these studies also throw light on the dynamic adequacy of such surgical shunts in patients with coarctation of the aorta.

Human coarctation may also be complicated by a persistent ductus arteriosus. In the series collected by Maude Abbott,[2] approximately 10 per cent of all patients with adult type of coarctation had an associated patent ductus arteriosus. The same proportion has been reported in cases of coarctation referred to the Mayo Clinic.[3] In most of these cases blood from the aorta was obviously shunted into the pulmonary artery. However, several cases have been reported[3–6] in which the flow of blood was apparently directed from the pulmonary artery to the aorta, the right ventricle acting as a "systemic ventricle." Douglas and associates[5] described a case of patent ductus arteriosus with the unusual features of cyanosis, right ventricular hypertrophy, and obstructive pulmonary vascular lesions. An aortic intimal lesion, the so-called "jet lesion," was present opposite the entrance of the ductus, and its structure was consistent with that of a reaction to mechanical irritation. On that basis, they concluded that at least for part of the cardiac cycle the pressure within the right ventricle equalled or exceeded that within the aorta, thus causing a flow of blood from the pulmonary artery to the aorta.

In another case, described by Edwards and

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co-workers,[6] the systolic pressure in the left leg varied from 98 to 102 mm. Hg, and the diastolic pressure ranged from 50 to 60 mm. Hg, which compared very favorably with the diastolic pressure of 45 to 50 mm. Hg in the upper arm. Necropsy revealed that the right ventricle equaled the left in thickness and the systemic collateral circulation was not well developed. The lumina of the intrapulmonary arteries and arterioles, as seen on microscopic examination, were greatly narrowed. In still another case, described by Taylor and associates,[3] the oxygen content of the femoral artery blood was low, although the femoral blood pressure was equivalent to that in the radial artery. The collateral circulation also was not developed in this case. This suggested a flow of blood from the pulmonary artery to the aorta. In order to determine whether dynamic conditions other than high pulmonary resistance and failure in the development of arterial collaterals might cause the right ventricle to propel blood through a patent ductus into the aorta below a constriction, an artificial shunt was made between the pulmonary and systemic systems and the effect of its opening during various degrees of aortic coarctation was studied.

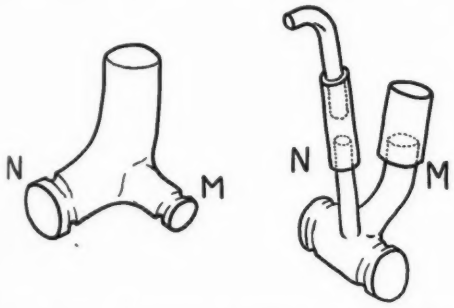

FIG. 1*A*. Pulmonary T-cannula. *B*. Aortic cannula.

METHODS

Aortic pressure pulses above and below the constriction and in the femoral artery were recorded as described in the preceding paper.[1] In experiments designed to study the effects of systemic shunts, the side tube of a glass cannula inserted into the aorta was connected with a subclavian artery. In experiments designed to study the effect of a patent ductus arteriosus, a pulmonary T-cannula, shown in figure 1*A*, was specially designed so that the blood might flow unobstructed to the left lung. The narrow side (M) was inserted into the distal side and the wider side (N) toward the pulmonary trunk side so that the lumen might correspond to the natural lumen of the vessel. An aortic-pulmonary shunt was made by connecting the aortic cannula by a short, wide plastic tube to the pulmonary T-cannula. In some of these experiments pressure pulses were also recorded immediately below the coarctation. To accomplish this an aortic cannula with two side tubes (Fig. 1*B*) was used, one side tube (M) for making the shunt and the other (N) for recording the pressure. Right ventricular pressures were secured in some experiments by means of a blunt needle (15 gage), introduced through the ventricular wall.

Many records were taken to determine the effects that opening of a shunt had on the aortic and femoral pressure pulses when varying degrees of coarctation existed.

RESULTS

Dynamic Changes Resulting from the Opening of a Subclavian-Aortic Shunt. Figure 2 shows the effects of opening the subclavian-aortic shunt on the aortic (upper curve) and femoral (lower curve) pressure pulses with severe degrees of coarctation. Segment *A* shows the normal relationship, segment *B* the effect of 80 per cent stenosis with the subclavian-aortic shunt closed. Due to the resistance to the flow of blood through the stenosis, the femoral pressures have fallen from 186 to 91 mm. Hg systolic, and from 116 to 81 mm. Hg diastolic. The pulse pressure was greatly reduced. The aortic systolic pressure, on the other hand, rose from 171 to 194 mm. Hg, and the diastolic pressure remained unaffected. The heart rate decreased from 151 to 144 per minute. Segment *C* shows the effect of opening the subclavian-aortic shunt. The aortic pressures diminished substantially from 194 to 178 mm. Hg systolic, and from 124 to 117 mm. Hg diastolic. The femoral pressures increased from 91 to 142 mm. Hg systolic, and from 81 to 107 mm. Hg diastolic. The pulse pressure increased greatly. The heart rate came back to normal. The contour of the femoral pressure curve, however, did not return to normal. The ascending and descending limbs still have a gradual slope, though less gradual than in segment *B*, and there is still no appearance of the dicrotic wave. The

summit of the curve, however, has become more peaked. It greatly resembles curves after moderate coarctation (see fig. 3*C* of previous paper). From a series of 10 experiments it was apparent that the subclavian-aortic shunt has reduced the load in the upper part of the body by reducing the pressures substantially, and has increased the flow to the lower extremities.

Dynamic Changes Resulting from Opening a Pulmonary-Aortic Shunt. Figure 3 shows a series of paired tracings illustrating the effects of opening an aortic-pulmonary shunt when various degrees of aortic coarctation exist. The two curves in each pair represent the aortic (upper) and femoral (lower) pressure pulses before and after opening the shunt. The pair of records *A* shows the pressure relationship with unconstricted aorta. The pair of records *B*, *C*, *D*, *E*, and *F* represent the effects of opening the shunt with 55, 65, 75, 85 and 90 per cent reduction of the aortic lumina. Normally, with the shunt closed, the aortic pressures were 105 mm. Hg systolic and 74 mm. Hg diastolic; the femoral pressures, 124 mm. Hg systolic and 68 mm. Hg diastolic. On opening the shunt, the aortic pressure pulse shows an increase in the gradient of the ascending limb. There is a late systolic collapse and the diastolic pressure becomes very low, resulting in a greatly increased pulse pressure. The femoral pulse shows an increased gradient of the ascending and descending limbs, resulting in a high systolic and low diastolic pressure with high pulse pressure. The dicrotic wave disappears on opening the shunt. With a moderate degree of coarctation in pair of records *B*, the general features are the same as in *A*, except that the femoral systolic pressure also falls to some extent. The aortic and femoral pulse pressures both become larger on opening the shunt.

With still greater degrees of stenosis in segments *C* and *D*, significant changes occur on opening the shunt. The systolic aortic pressures now increase considerably and the diastolic pressure first falls (pair of records *C*). But, as the degree of stenosis is increased, the diastolic pressure also increases (pair of records *D*). The femoral pressure pulses at this stage assume the typical appearance of the coarctation pulse. Opening of the shunt reduces both the systolic and diastolic pressures, but there are no significant changes in the contour of the curve and in pulse pressure. The pair of records (*E*) with 85 per cent stenosis shows the same pressure relationships in aortic curves as in *D*, but, though the femoral pressures are less on opening the shunt, the pulse pressure is definitely increased from 2 to 7 mm. Hg. The pair of records *F* shows the effect with 90 per cent stenosis. With the aortic-pulmonary shunt

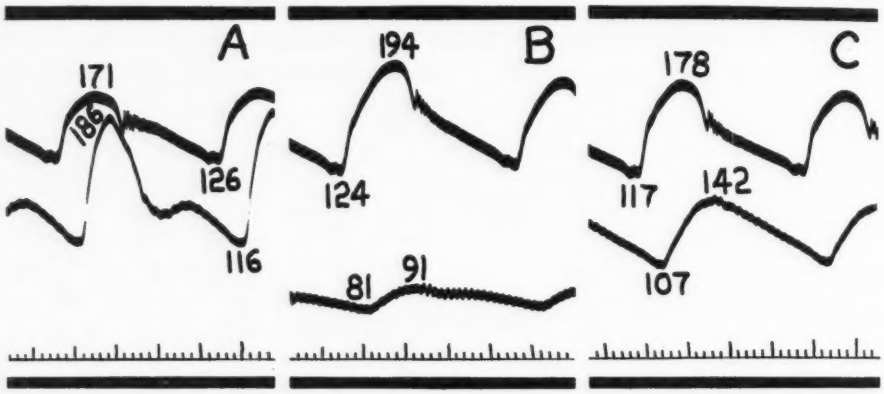

FIG. 2. Effects of opening the subclavian-aortic shunt on the aortic (upper curve) and femoral (lower curve) pressure pulse contours after severe degrees of coarctation. Segment *A* shows the normal relationships. Segment *B*, the effect of 80 per cent stenosis with the shunt closed, and segment *C*, after opening the shunt.

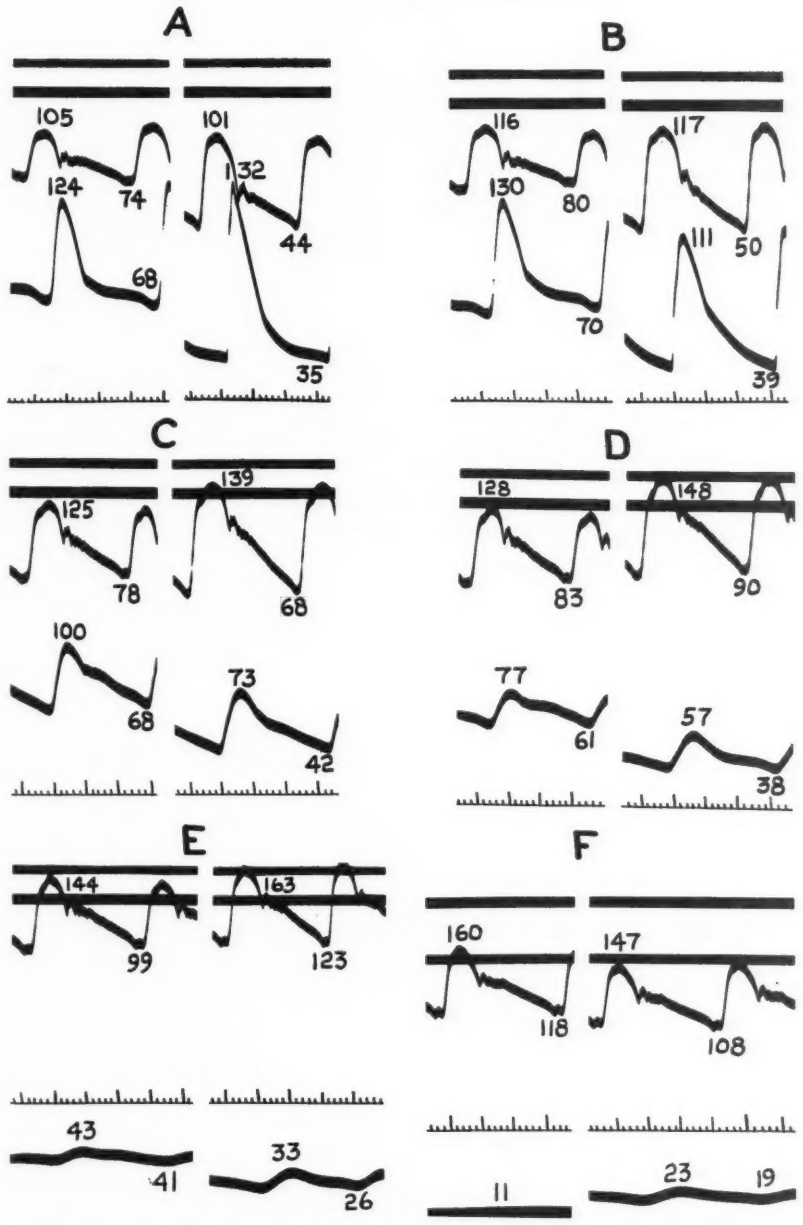

FIG. 3. Effects of opening an aortic-pulmonary shunt after various degrees of coarctation. Segment *A* shows the pressure relationships with unconstricted aorta. Segments *B*, *C*, *D*, *E*, and *F* represent the effects of opening the shunt with 55 per cent, 65 per cent, 75 per cent, 85 per cent, and 90 per cent reduction of the aortic lumen. The two curves in each segment represent the pressures and pulse contours before and after opening the shunt.

closed, the femoral pulse pressure has become zero and the mean pressure has decreased to 11 mm. Hg, indicating that the flow through the stenosis had been reduced to a mere trickle. Upon opening the shunt, there is a fall in the aortic pressure, while the femoral pressure now increases from 11 to 23 mm. Hg systolic and shows a definite pulsation.

In order to study the effects of opening a shunt during various degrees of acute coarctation on the right heart, pressures were also recorded from the right ventricle. Figure 4 shows segments of such records, together with pressure pulses from the aorta above the stenosis, and from 137 to 141 mm. Hg, the diastolic pressure is reduced from 73 to 56 mm. Hg, resulting in a greatly increased pulse pressure. The gradient of the aortic pressure curve becomes steeper and the pressures below the shunt are further reduced, systolic from 92 to 52 mm. Hg, and diastolic from 74 to 38 mm. Hg. On the curve are superimposed marked vibrations due to the turbulence created by the large increase in the velocity of ejection from the left ventricle. The contour of the right ventricular pressure curve is not changed, but maximal pressure has increased from 43 to 50 mm. Hg systolic, and the initial tension from 8 to 9 mm. Hg. The dura-

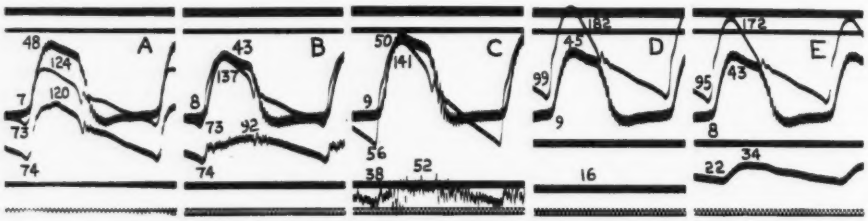

FIG. 4. Effects of opening a shunt during various degrees of acute coarctation on the right ventricular pressures (upper curves in segments *A*, *B*, *C*, and middle curves in segments *D* and *E*), together with pressure pulses from the aorta above the stenosis (middle curves in segments *A*, *B*, *C;* upper curves in segments *D* and *E*) and below the stenosis and shunt (lower curves). Segment *A* shows the normal relationships with aorta unconstricted. Segment *B*, effect of 70 per cent stenosis of the aortic lumen. Segment *C*, after opening of the shunt, and segments *D* and *E*, before and after opening the shunt with 93 per cent constriction of the aorta.

immediately below the stenosis and shunt. Segment *A* shows the normal relationship with the aorta unconstricted. The pressures in the aortic arch and in the aorta below the shunt are essentially the same, as are also their pulse contours. The right ventricle shows initial and maximal pressures of 7 and 48 mm. Hg respectively. Segment *B* illustrates the effect of 70 per cent stenosis of the aortic lumen. The aortic systolic pressure above the stenosis has risen as before, the diastolic pressure remaining the same. The pulse contour of the thoracic aortic pulse below the coarctation (lower curves) has the murmur graphically recorded. The right ventricle shows only a slight increase of initial pressure. Segment *C* depicts the effect which follows opening the aortic-pulmonary shunt. The aortic systolic pressure is increased slightly tion of ejection phase is slightly increased in segment *C* as compared with *B*.

Segment *D* shows the effect of 93 per cent stenosis of the aorta with the shunt closed. As seen before, the aortic pressure has risen to a very high level and the aortic pressure below the coarctation has zero pulse pressure and a mean pressure of only 16 mm. Hg. The right ventricular initial and maximal pressures are slightly higher than in the segment *B* with 70 per cent stenosis. Upon opening the shunt in segment *E*, the aortic pressures fall and the aortic pulse pressure becomes slightly reduced. On the other hand, the femoral systolic pressure is increased from 16 to 34 mm. Hg and the pulse pressure from 0 to 12 mm. Hg.

Since the femoral pressure wave is obviously due to right ventricular action, the changes in

the right ventricular pressure curves are especially important. It will be noted that the right ventricle accomplishes its ejection into the systemic circuit during nearly complete occlusion of the aorta with an actual slight reduction of initial and maximal pressures. The shunt was left open for 3 hours and 45 minutes to ascertain whether there are any further changes in behavior of the right ventricle and femoral pressures suggestive of other compensatory reactions, but none were found.

Discussion

The experiments on effects of opening a subclavian-aortic shunt were designed primarily to simulate and study the efficiency of natural shunts that develop in the body in individuals with aortic coarctation, and secondarily to determine the dynamic adequacy of artificial surgical shunts in alleviation of coarctation in human subjects. The results presented show clearly that a subclavian-aortic shunt is helpful in several respects, despite the fact that the femoral pressure pulses do not recover a normal form.

In the first place, the presence of such a shunt reduces the hypertension central to the coarctation. This is not wholly due to diminution in aortic resistance, for were this the case diastolic pressure should have declined more than systolic and the pulse pressure should have increased after opening of a shunt, not decreased, as in these experiments (fig. 2*B*, *C*). The predominant fall in systolic pressure and decrease in pulse pressure indicate a decrement in stroke volume of the left ventricle. The mechanism by which this is accomplished has been established by Wiggers and Katz (figs. 8 and 9)[7] through registration of ventricular volume curves before and after decompression of the aorta. When aortic resistance is diminished the left ventricle empties itself more completely for a few beats, thereby reducing the residual blood and diastolic size. As soon as this eventuates the systolic discharge becomes less than during a state of elevated pressure. Such an automatic adjustment of the stroke volume of the left ventricle explains the reduction in pulse pressure and predominant decline of systolic pressure.

In the second place, the existence of a shunt increases the flow into the distal aorta to such an extent that diastolic femoral pressure is elevated considerably. This indicates that a good drainage reservoir exists for maintaining a continuous flow of blood through tissues below the coarctation, i.e., during diastole as well as systole.

In the third place, the persisting deviations of the femoral pulse from normal—slower rise and fall and absence of dicrotism—are not as serious dynamically as they seem. Excessive damping of the central pressure wave is responsible for the slower rise and to some extent for the more gradual fall. When the forceful impact of ventricular ejection is not transmitted to the lower aorta, as in coarctation, the blood column is not set into oscillation; no standing wave is created, the rising limb of the femoral pulse is not accelerated, systolic pressure does not overshoot, and the descending limb is not deformed by a dicrotic notch and wave. It more truly represents the gradual degradation of pressure energy to flow during late systole and diastole than does the normal femoral pulse. The deviations from a normal form of the femoral pulse are therefore less important than the elevation of diastolic pressure after opening a shunt.

The physical mechanism by which the rise of femoral pressure becomes steeper and greater after opening a systemic shunt still requires analysis. The rise is always smooth and steeper from the start; there is never an anacrotic halt or suggestion of summated waves on the rising pressure limb. This strongly suggests that the pressure waves entering the lower aorta through a stenotic aorta and the subclavian shunt have so little time difference that they combine to produce a smooth rapid elevation from the start. This is dynamically important in that turbulence is probably avoided.

On dynamic grounds, therefore, the surgical creation of subclavian-aortic shunts[8, 9] would seem to constitute sound procedure for creating an adequate blood flow below the constriction

and in alleviating the state of hypertension above it. Everyone is agreed that the ideal operation of clinical coarctation is one in which the stenotic area is excised and the proximal or distal ends of the aorta are united by suture as performed by Crafoord and Nylin,[10] and Gross and Hufnagel.[11] Unfortunately, there are some instances in which this does not appear to be feasible, either because the constricted area in the aorta may be too extensive or the left subclavian artery may arise too close to the localized area of constriction. The question has been raised as to whether one should employ the left subclavian to by-pass the point of stenosis if the ideal operation cannot be performed. These experimental results support the conclusion of Bing and associates,[12] that the subclavian-aortic anastomosis does reduce the load to the upper part of the body and substantially increases the amount of blood to the lower part of the body.

Opening of an aortic-pulmonary shunt reduplicates the dynamic condition of humans in which the ductus arteriosus persists without a complicating coarctation. The primary effect on the arterial pressure pulses illustrated in figure 3*A* is due to lowering of peripheral resistance; diastolic pressure declines predominantly and the pulse pressure increases in the aorta. To this is added the almost immediate increase in systolic discharge of the left ventricle; the blood which leaves the aorta by way of the pulmonary shunt quickly augments the return of blood to the left heart and is disposed of by augmentation of stroke volume. The magnitude of this flow is indicated by observations of Eppinger and co-workers[13] that 40 to 75 per cent of the left ventricular output may pass through a patent ductus. This brusque increase in systolic discharge accentuates femoral pressure by causing a great overshoot of systolic pressure, but the reduced aortic resistance occasioned by the aortic-pulmonary shunt results in a marked drop in diastolic pressure, much as in cases of A-V fistula and aortic insufficiency. As in these cases also, the distinctive feature is the loss of the dicrotic wave.[14] The picture does not change significantly when an aortic-pulmonary shunt is complicated by a degree of aortic stenosis up to 55 or 60 per cent of the aortic lumen (fig. 3*B*).

As aortic coarctation becomes more severe the resultant changes of systolic discharge and aortic resistance caused by opening of a shunt alter continually. In this connection it is important to remember that as far as effects on aortic pressure are concerned, change in resistance caused by opening a shunt is not determined alone by the caliber and length of the shunt and the pressure in the aorta below the coarctation; resistance is a physical ratio of pressure: flow. While changes in resistance are not actually determinable, their relative importance in accounting for aortic pressure changes can be inferred from alterations that occur in aortic diastolic pressure on opening the shunt. Since diastolic pressure is reduced when a shunt is opened in cases of mild aortic constriction (fig. 3*B*, *C*), but increased when constriction is severe (fig. 3*D*, *E*), it is obvious that reduction in resistance plays a recognizable role only when the degree of constriction is moderate (about 65 per cent reduction). Judging from the increase in aortic systolic and pulse pressures (fig. 3*D*) after opening of a shunt, augmentation of systolic discharge continues to be the dominant factor until an extreme state of coarctation exists. Finally, however, the flow of blood through the shunt is so far reduced—or even reversed—that systolic discharge becomes less and consequently aortic pressures fall on opening the shunt (fig. 3*F*).

Even in fairly marked aortic coarctation, opening of the shunt has comparatively little effect on the femoral pulse except to reduce systolic and diastolic pressures and to smooth the dicrotic wave (fig. 3*C*, *D*). However, when femoral pressure has declined to very low levels (fig. 3*E*, *F*), an augmentation of the pressure pulse is produced by a reversal of flow. Attention may be called to the fact, apparent from the curves *C*, that 65 per cent coarctation with complicated patent ductus is much more serious than a pure case of coarctation. The femoral pressures and pulse contours with 65 per cent stenosis and with the shunt open, resemble a

stenosis of about 75 per cent with the shunt closed. The pair of curves *E* with 85 per cent stenosis still show reduced femoral pressures on opening the shunt, but the femoral pulse pressure is increased. The reduced femoral pressure is explained by the fact that blood is still flowing from the aorta to the pulmonary artery on opening the shunt, thus lowering the femoral pressures. The fact that pulse pressure is increased strongly supports the inference that the right ventricle is pumping blood into the aorta during some part of the cardiac cycle. This would have been more certain if the femoral pressure curve had shown a second hump on the ascending limb. In *F*, however, with 90 per cent coarctation the aortic pressures fall and the femoral pressures rise on opening the shunt. In this case, the right ventricle was certainly pumping blood into the aorta below the coarctation.

The manner in which the right ventricle responds when blood is suddenly shunted into the pulmonary circuit can be deduced from changes in the right ventricular pressure curves. The pulmonary arterial pressure against which the right ventricle is required to eject its blood is probably raised to nearly the same level as in the aorta below the constriction. In figure 4 the pressure varies from 38 mm. Hg diastolic to 52 mm. Hg systolic. The right ventricular pressure must obviously be raised above this level in order to expel its contents. In figure 4*C* this is the case during the early phase of ejection but during the later portion of ejection the aortic pressure tends to exceed right ventricular pressure slightly. This probably augments the residual volume of the right ventricle and is responsible for the slight elevation of initial tension seen in this record. However, the right ventricle at no time appears to be under increased strain such as follows pulmonary stenosis, for example.

The normal right ventricle acts as a systemic ventricle only when an intense degree of aortic constriction exists and the pressure in the distal aorta falls to a level below that in the pulmonary artery. Despite repeated trials, this proved successful only after arterial pressure had been reduced to a low constant level, as in figure 4*D*. Since opening the shunt decreases pulmonary resistance, the transfer of right ventricular blood is effected with an actual slight decline of maximal right ventricular pressure. As a result also, its residual volume decreases and initial tension tends to decline slightly, as in figure 4*E*. In short, the right ventricle is relieved of strain and the commonly accepted determinant for provoking its hypertrophy is absent. It is obvious that other factors may enter into clinical cases. The suggestion has been made on deductions from necropsy studies[6] that in clinical cases the excess flow of blood through the pulmonary system occasioned by a patent ductus may gradually cause sclerosis of pulmonary vessels. It is by no means clear that such a "cause and effect" relation exists; the sclerotic process may be wholly unrelated to the dynamic disturbances. However, regardless of the way in which pulmonary arterial sclerosis is induced, the increased resistance thus occasioned may react functionally on the right ventricle to cause its hypertrophy. Proof of this attractive hypothesis awaits evidence by catheterization studies that initial tension is unquestionably elevated in the right ventricle. It is quite possible that ejection of blood by such a hypertrophied right ventricle against a higher pulmonary resistance will be able to transfer blood to the aorta when pressures are at higher levels than in acute experiments.

Summary

1. To elucidate the purely dynamic effects of collateral arterial circuits in aortic coarctation, an artificial shunt was made between the subclavian artery and the aorta distal to the constriction and pressure pulses were recorded by optical manometers from the aortic arch and the femoral artery.

2. Analysis of pressure pulses revealed that with moderate degrees of aortic constriction, opening of a subclavian-aortic shunt causes the following changes: (a) Above the constriction systolic pressure is reduced more than diastolic, hence the diminution in hypertension is not

wholly determined by decrease in aortic resistance, but significantly also by an automatic reduction in systolic discharge. (b) Below the constriction, as exemplified by the femoral pressure pulse, the systolic and diastolic pressures are elevated and the pulse pressure increases, but the form of the pulse does not return to normal; it maintains a more gradual ascending and descending limb.

3. The persisting deviations of the femoral pulse from normal are not as serious as they seem. The fact that diastolic pressure is markedly elevated indicates that enough blood reaches the lower aorta to make it a good diastolic drainage reservoir from which a continued blood flow through tissues can be maintained. These favorable effects combined with the reduction in hypertension above a stenosis and the relief of the left ventricle from strain make the creation of an artificial subclavian-aortic shunt a procedure which is dynamically sound.

4. In order to study the dynamic alterations that result from the coexistence of a patent ductus arteriosus and aortic coarctation, an artificial shunt was made between the aorta and pulmonary artery just below the coarctation, and the effect of opening such a shunt on aortic, femoral, and right ventricular pressure pulses was determined when the aorta was constricted to different degrees.

5. Analysis of such records revealed that with moderate degrees of coarctation, i.e., up to 55 to 60 per cent of the aortic lumen, opening of the shunt causes a predominant fall of diastolic pressure and a marked increase in pulse pressure above the coarctation. This is primarily due to the reduction in aortic resistance. However, the increased return of blood to the left heart very quickly augments the systolic discharge of the left heart so that systolic pressure remains essentially unchanged or actually rises. The increased systolic discharge also accentuates systolic femoral pressure, but the reduced aortic resistance causes a rapid decline of pressure to a low level, much as in aortic insufficiency or an arteriovenous fistula.

6. With more severe degrees of coarctation, the presence of a shunt alters the relative roles that reduction in aortic resistance and increase in systolic discharge play in determining aortic systolic and diastolic pressures. Only in cases of extreme degrees of coarctation does the presence of a shunt cause the stroke volume to diminish and aortic pressures to fall. This occurs when the blood flow through the shunt is reversed from the pulmonary to the systemic vessels.

7. The presence of an aortic-pulmonary shunt has no dynamic effects on the right ventricle of a normal dog by virtue of which pulmonary pressures can be raised sufficiently to exceed aortic pressures below the coarctation until occlusion of the aorta is nearly complete. The possibility that the right ventricle acts as a systemic ventricle in clinical cases through coincident increase in pulmonary resistance is not excluded by these experiments.

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Hepatorenal Factors in Circulatory Homeostasis

IV. Tissue Origins of the Vasotropic Principles, VEM and VDM, Which Appear during Evolution of Hemorrhagic and Tourniquet Shock

By Ephraim Shorr, M.D., Benjamin W. Zweifach, Ph.D., Robert F. Furchgott, Ph.D., and Silvio Baez, M.D.

Studies were carried out in dogs and rabbits subjected to hemorrhagic and tourniquet shock to determine the tissue origins of two newly described vasotropic principles, VEM and VDM. The vasoexcitor principle, VEM, predominates in the blood during the initial compensatory stage and was traced to the kidney. The vasodepressor principle, VDM, prevails during the decompensatory phase and was found to originate in the liver, skeletal muscle and spleen. During the decompensatory phase, there was a progressive deterioration of the hepatic mechanisms for inactivating VDM. Sequential tissue hypoxia during shock is probably responsible for the formation of these vasotropic principles and for the deterioration of the hepatic VDM inactivation system. Special emphasis is placed on the effects of local concentrations of VDM within the liver and on the resultant diversion of blood from the general circulation into the splanchnic viscera.

STUDIES in this laboratory, over the past several years, have been concerned with the participation of specific humoral vasotropic factors in the deranged circulatory hemodynamics of experimental hemorrhagic and traumatic shock. These investigations have led to the development of a concept of experimental shock, especially with respect to the phenomenon of irreversibility, which has already been presented in several publications of a descriptive character.[1,2] It is the purpose of the present series of papers to provide the experimental evidence from which this concept developed.

When these studies were inaugurated the concepts of shock then current failed to provide an adequate explanation for many of the phenomena of both clinical and experimental shock. It was the consensus that the ultimate collapse of the organism was the consequence of peripheral circulatory failure.[3] It was also appreciated that a differentiation must be made between the factors which initiate and those which perpetuate the shock syndrome.[4] Among the factors considered to be involved were fluid loss,[5] neurogenic influences,[6] changes in capillary permeability[7] and toxic and humoral agents.[8] However, the relative importance of these factors and their specific influence in different states of shock remained unclear. The earlier postulate by Cannon,[5] Bayliss and others that deleterious principles resulting from tissue damage initiated the syndrome of traumatic shock and contributed to the fatal outcome, had fallen into disfavor on two scores. There was no clear-cut evidence implicating specific toxic factors, and direct proof was furnished that the initiation of the syndrome was in large measure attributable to a reduction in blood volume secondary to the extravascular loss of fluid in the traumatized limb.[9] This latter finding, as well as the favorable effects of blood replacement therapy, served to focus attention on the reduction in the effective blood

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volume and its immediate circulatory consequences, to the neglect of other factors. However, although the fluid-loss concept per se seemed adequate to explain the initiation and the early manifestations of the shock syndrome, such as hypotension and vasoconstriction, it threw no light on either the nature of the compensatory mechanisms involved or the reasons for their deterioration as the shock syndrome progressed. The latter phenomenon is of particular importance in relation to the development of increasing refractoriness to fluid replacement therapy and eventual irreversibility, a condition which occurs not only in clinical shock but which can be regularly produced in animals by standard experimental procedures.

The fluid-loss concept failed to resolve other areas of uncertainty such as the decreased tolerance to blood loss and hypotension in traumatic as compared with hemorrhagic shock, and the death from tourniquet shock of animals whose limbs were tightly taped to prevent significant fluid loss. Attempts have been made to explain the differences between hemorrhagic and traumatic shock on the basis of changes in blood viscosity,[10] an increased participation of the neurogenic vasoconstrictor component,[11] and the phenomenon of sludging.[12] No conclusive evidence was provided for a critical influence of any of these factors.

These inadequacies prompted investigation of the hemodynamic effects of a variety of known agents of tissue origin with a view to determining whether a definite role in the shock syndrome could be assigned to any of these substances. Of the many studied—histamine, potassium, kallikrein,[13] adenylic acid, adenosine triphosphate[14] and acetylcholine—none produced effects which per se related them directly to the peripheral vascular reactions characteristic of either the initial or the terminal decompensatory phases of experimental shock. Other studies revealed numerous alterations in the chemical composition of the blood which apparently reflect the relatively anaerobic character of metabolism during shock[15,16]; however, it was not possible to establish a causal relationship between any of these changes and the specific circulatory derangements associated with the development of irreversibility.

The direction of our own studies was set by the observation of Zweifach, Chambers and their associates,[17,18] using the vascular reactions of the exteriorized omentum and mesentery as an index, that the shock syndrome in anesthetized animals subjected to prolonged hemorrhagic hypotension proceeds in two stages, an initial compensatory and a subsequent decompensatory stage. The initial compensatory phase is characterized by a hyperreactive condition of the terminal vascular bed. This hyperreactivity is manifested by an increase in the intermittent constrictor activity (vasomotion) of the metarterioles and precapillaries; and its extent can be conveniently measured by noting the enhanced responsiveness of these muscular vessels to the topical application of epinephrine. The capillary ischemia which results from the accentuation of the constrictor phase of vasomotion and the consequent restriction of blood flow in the capillary bed to thoroughfare channels, the metarterioles, serve to maintain an active venous return of blood from the tissues despite a reduced blood volume. The ability to respond satisfactorily to transfusion seems to depend upon the maintenance of this type of peripheral vascular activity. However, with the onset and prolongation of more drastic hypotension, vascular changes gradually appear in the splanchnic areas visualized which are antagonistic to the compensatory vasomotor adjustments prevailing in the initial stage, and which eventually disrupt the peripheral circulation. During the decompensatory stage there is a progressive reduction of epinephrine reactivity and a slowing and finally complete suppression of spontaneous vasomotion in the terminal arterioles and precapillaries with resultant relaxation of precapillary sphincters. The predominance of decompensatory influences on the peripheral circulation now leads to an increasing diversion of blood into the capillary side channels from which it is inefficiently returned to the active circulation because of the reduced blood pressure. Once this decompensatory hyporeactive phase has fully developed, a state of irreversibility or failure to respond to

transfusions is reached. That blood-borne factors are responsible in large measure for the vascular episodes described above was suggested by the passive transference of corresponding effects to similar vessels in the mesoappendix of normal test rats.[19] Thus, blood obtained from animals when the mesenteric vessels are hyperreactive exerts vasoexcitor effects which are manifested by an increased reactivity to topical epinephrine. On the other hand, blood obtained when the mesenteric vessels are hyporeactive exerts a vasodepressor effect in the test rat characterized by a reduction in responsiveness to epinephrine.

This new and important contribution to the theory of shock provided the stimulus for the present studies which were designed to explore the mechanisms responsible for the occurrence of these humoral principles, and to set up appropriate experimental conditions for revealing their sites of origin in specific tissues as well as the environmental and cellular factors concerned with their formation and inactivation. A correlation of in vitro and in vivo phenomena was made possible by the rat mesoappendix test of Zweifach and Chambers[20] for assaying the vasoexcitor and vasodepressor principles.

Before presenting the experimental data it may be appropriate to sketch the broad outlines of our findings as a background against which these data may be projected.[1, 2] It was found that the vasoexcitor, VEM, which predominates in blood during the initial compensatory phase of shock, had its origin in the kidney and chiefly in the cortex. The vasodepressor, VDM, which predominates during the decompensatory phase was found to arise from the liver, skeletal muscle and spleen.

The mode of origin of these vasotropic principles was investigated by in vitro procedures which permitted a more precise evaluation of the influence of specific environmental factors. Both VEM and VDM were found to be products of anaerobic metabolism; neither was formed by normal tissues under aerobic conditions. Furthermore, the tissues to which the origins of VEM and VDM were traced in vivo were also those in which their formation took place in vitro.

Finally, it was noted that under aerobic conditions, normal liver possessed the property of inactivating VDM, from whatever source obtained; and that normal renal cortex exhibited an analogous capacity to inactivate VEM under similar conditions. The hepatic VDM inactivation mechanism was found to be preserved during the hyperreactive phase of shock but to undergo a gradual deterioration to total loss during the progression of the hyporeactive stage. This deterioration of the VDM inactivation system could also be induced in vitro by a prior exposure of liver tissue to anaerobiosis.

From these and other correlative studies a concept of shock has been formulated and will be developed in this series of papers. This concept rests on three main types of experimental observations: the sequential appearance of compensatory and decompensatory behavior in the terminal vascular bed during the evolution of the shock syndrome; the regular association of these vascular episodes with the humoral predominance of the renal vasoexcitor, VEM, and the hepatic vasodepressor, VDM, respectively; and the metabolic alterations during shock in the renal and hepatic mechanisms concerned with the formation and inactivation of these vasotropic principles. This concept would relate the initial compensatory vascular reactions to the appearance of VEM in the blood as a consequence of renal hypoxia. The subsequent decompensatory vascular behavior, which culminates in irreversibility, is attributed to the appearance and predominance of the hepatic vasodepressor, VDM, as a consequence of the hypoxia of the liver resulting from drastic hypotension. Finally, emphasis is placed on the crucial importance, for the development of irreversibility, of the deterioration during the hyporeactive stage of the hepatic VDM inactivation mechanism, without which the peripheral circulation cannot be liberated from the decompensatory effects of VDM.

This concept does not exclude the participation of a variety of other contributing factors of metabolic, humoral or nervous origin, but

would assign a major role to these newly described vasotropic principles and the mechanisms underlying their formation and destruction by virtue of their relation to specific peripheral circulatory phenomena observed in experimental shock.

The present report will deal largely with the sites of origin as revealed by experiments on hemorrhagic and tourniquet shock. The papers to follow will present the data relating to the mechanisms of formation and inactivation of these vasotropic factors.

Methods

A. *Rat Mesoappendix Test*

The rat mesoappendix test originally developed by Zweifach and Chambers made it possible to follow changes in the vasotropic activity of the blood during the development of the shock syndrome. A complete description of the test is given in a separate publication.[20] The appearance of vasoexcitor or vasodepressor substances in the blood or in tissue extracts can be determined by injecting the test samples intravenously into normal rats and observing the changes which occur in the responsiveness of the terminal arterioles and precapillaries of the mesentery to topically applied epinephrine.

The reactions of the terminal vascular bed are studied by direct microscopic observation of the exteriorized mesoappendix (mesocecum) of young rats weighing from 100 to 125 Gm. The animals are anesthetized with sodium pentobarbital, 3.5 mg. per 100 Gm. of body weight, administered intramuscularly. The exteriorized mesentery is gently draped over a glass horseshoe and moistened by irrigation with a Ringer solution containing 1 per cent gelatin. The temperature of the solution is thermostatically controlled so that it drips upon the mesoappendix at 37.5 to 38.0 C. For the test, a terminal arteriole, 15 to 25 microns in diameter (the metarteriole type whose precapillary offshoots lead directly into the network of true capillaries) is selected. The *minimal effective* or *threshold* concentration of epinephrine is then determined. This represents the lowest concentration of the drug which, on being applied to the surface of the mesentery, produces a moderate narrowing of the arteriole, sufficient to slow appreciably the blood flow in its capillary branches. It is best to begin with subthreshold concentrations of epinephrine, of about 1:10,000,000 to 1:20,000,000 and to increase the concentration gradually until an effective range is attained. In the anesthetized rat the threshold concentration of epinephrine usually lies between 1:5,000,000 and 1:6,000,000. Under standardized conditions, the epinephrine value characteristic of a given arteriole will remain relatively unchanged for at least one to two hours. The injection of test samples containing active vasotropic principles will shift the epinephrine threshold. The degree and nature of this change in epinephrine responsiveness serves as an index of the vasotropic activity of the injected material. The samples which are to be assayed are injected into the tail vein, a maximum of 0.5 cc. per 100 to 125 Gm. of rat being used.

Vasotropic substances with which this study is concerned are classified in two categories: *potentiators* (vasoexcitor material or VEM) or *inhibitors* (vasodepressor material or VDM) of the constrictor response to epinephrine. Substances which produce no detectable change in the reactivity of the peripheral vessels are designated as *neutral*. A comparison of the vasotropic activity of different samples is made either by noting the duration of the resultant vascular effect, or, in addition, by determining at approximately three minute intervals the precise concentration of epinephrine needed to bring about the control type of vascular contraction. In the present study vasodepressor materials were usually assayed by determining the interval over which vessels remained refractory to the control concentration of epinephrine. The time noted was from the injection of the test sample until the vessels returned to a completely normal response. In quantitating the vasoexcitor material the duration of the increased sensitivity to epinephrine was noted and, in addition, the magnitude of the hyperreactivity was measured by determining the dilutions of epinephrine which were just adequate to bring about the critical response of the arteriole. This latter procedure prevented the undesirable sensitization of the arterioles which is produced by repeated applications of epinephrine in higher than threshold concentrations.

An example of the procedure used in assaying a vasodepressor sample is given in figure 1. In this test the arterioles remained refractory to a threshold concentration of 1:2 million for 28 minutes. This sample was therefore classified as a 28 minute VDM. A protocol in which tests were made to determine the precise concentration of epinephrine needed to produce the control type of arteriolar response is illustrated in figure 2. The area between the base-line and the curve, a function of both *duration* and *intensity*, gives a more precise measure of VDM activity.

A test for vasoexcitor material is illustrated in figure 3. In this instance it was necessary to dilute the original threshold concentration of epinephrine (1:2 million) sixfold to obtain the same degree of vasoconstriction as during the control period. The epinephrine response gradually returned from this peak of hyperreactivity to the control level.

The usefulness of the rat mesoappendix test lies in the extreme sensivity of the peripheral blood vessels to substances circulating in the blood. In setting up the rat mesoappendix preparation, various pro-

cedures, such as excessive anesthesia and handling of the exposed tissue, reduce the reactivity of the

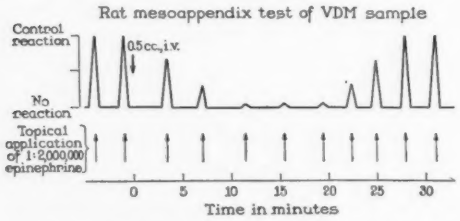

FIG. 1. Diagram of VDM assay based on the duration of the peripheral vascular effect induced in rat mesoappendix preparation. The graph depicts the progressive loss of reactivity to epinephrine in terminal arterioles of test rat on intravenous injection of VDM blood sample (experiment 19, table 1, dog C16, serum). The degree of arteriolar constriction elicited by epinephrine is indicated by the height of the peak above successive small vertical arrows, each representing a separate application of epinephrine. Approximately two to four minutes elapsed between each epinephrine application. Within seven minutes after injection of blood sample, the arteriolar response to epinephrine was almost completely obliterated. The control type of response did not reappear until 28 minutes had elapsed. This sample therefore assayed as a 28 minute VDM.

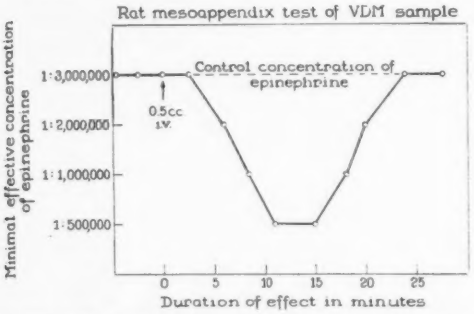

FIG 2. Method of quantitating VDM activity based on both duration and intensity of vascular effect produced. Each small circle represents a separate epinephrine application, and at each point the precise concentration of epinephrine required to produce the control type of arteriolar constriction was determined. The blood sample (heparinized plasma) was obtained from dog D57 (experiment 28, table 1). The shape of curve, its depth and the area between it and the base line, provide the indices for quantitating VDM activity. This sample assayed as a strong VDM of 24 minutes duration.

blood vessels to epinephrine. For this reason, every precaution should be taken to maintain only basal levels of anesthesia and to approximate as closely as possible normal conditions in the test preparation. It is essential to rule out atypical vascular effects due to factors other than VDM and VEM. These are produced by a variety of factors such as excess potassium ion, histamine and toxic substances originating from cellular breakdown. Such substances have untoward effects on the vascular system as a whole and thereby interfere with the evaluation of the peripheral vasotropic actions of VEM and VDM. When these precautions are observed, serum and heparinized plasma from normal animals give neutral rat tests, as do saline washes of normal tissues after clarification by centrifugation.

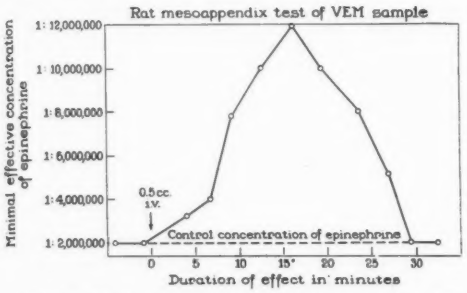

FIG. 3. Method used to grade VEM activity. The concentration of topically applied epinephrine required to produce the control type of arteriolar constriction was determined at intervals of about three to five minutes. Each small circle in graph represents a separate epinephrine application. Blood plasma used in test was from dog D114 (experiment 3, table 1). Following injection, arterioles of test rat became progressively more hyperreactive and required correspondingly lower concentrations of epinephrine to produce control type of arteriolar constriction. At peak of VEM effect, arterioles responded to a sixfold dilution of control concentration of epinephrine. This sample was therefore graded as VEM 6×29 minutes.

B. *Production of Hemorrhagic and Traumatic Shock*

Tourniquet shock was studied in rabbits and both tourniquet and hemorrhagic shock in dogs. Hemorrhagic shock was induced under sodium pentobarbital or, occasionally, Seconal anesthesia (25 to 30 mg. per Kg.) by graded bleedings according to the procedure suggested by Wiggers and Werle[21] for producing a state refractory to blood replacement therapy. Traumatic shock was produced in anesthetized dogs by applying rubber tourniquets as high as possible about the hind limbs so as to occlude both the arterial and venous circulation. Occlusion of the circulation for 8 to 10 hours invariably produced fatal shock when the tourniquets were released. In the rabbit, complete vascular occlusion of the hind limbs for four to six hours con-

sistently resulted in fatal shock following release of the tourniquets.

Blood pressure was recorded in the dog with a mercury manometer by cannulation of the femoral or carotid artery. No record of blood pressure was made in rabbits, the tissues and blood samples being removed for study when the animals were obviously in a state of circulatory collapse. Blood samples for testing were taken at intervals from either the jugular or femoral veins. Heparinized plasma or serum was used in the rat mesoappendix test. Tests were made within two to three hours after collection of the blood samples, which in the interval were kept in cracked ice in small Dewar flasks.

C. *Preparation of Saline Washes of Tissues for Bioassay*

The animals were sacrificed at appropriate times during the hyperreactive (compensatory) and hyporeactive (decompensatory) stages of shock, and various tissues removed. The tissues were immediately prepared as for microrespiration experiments. Liver, cardiac muscle, spleen and kidney cortex were sliced thinly to permit maximal diffusion. Thin sheets of smooth muscle were obtained by dissection from the wall of the small intestine. Individual fibers of skeletal muscle were dissected in situ from the hind limbs of dogs. The tissues were then placed in physiologic saline which was chilled in order to depress further metabolic activity, and thoroughly agitated for five to seven minutes. The ratio of tissue to saline was generally 1 to 5. The tissue washes were centrifuged and the clear supernatants kept chilled in Dewar flasks until tested. For the vasotropic assay, 0.5 cc. of the tissue wash was injected into the test rat.

D. *Terminology*

Throughout the paper, the terms VEM and VDM are used as abbreviations for *vasoexcitor* and *vasodepressor* material, respectively. The terms do not refer to effects on blood pressure or over-all caliber changes of the large blood vessels but are specifically defined with respect to the constrictor response of the terminal arterioles and precapillaries to topically applied epinephrine. The shock syndrome is differentiated on the basis of the two major types of peripheral vascular behavior which are regularly found to occur during the evolution of the syndrome under the experimental conditions employed. The term *hyperreactive* is applied to the initial phase of compensatory vascular hyperreactivity, which is associated with the presence of VEM in blood and with reversibility to fluid replacement therapy. The term *hyporeactive* refers to the subsequent decompensatory type of vascular hyporeactivity which is associated with VDM predominance in blood and the progressive development of refractoriness to fluid replacement therapy. It should be pointed out that inasmuch as the vessels were not visualized in most of the experiments, the basis for this differentiation rests on the presence of VEM or VDM in the blood as determined by the rat mesoappendix test. The justification for a differentiation on this basis has, however, been securely established by previous studies[17] which have shown the temporal association between these vasotropic substances in blood and the corresponding type of peripheral vascular behavior.

In addition to the studies of the vasotropic content of blood and tissues, data were also obtained on the influence of shock on the oxygen consumption of liver and kidney, on the aerobic inactivation of VDM by liver in vitro, and on the capacity of kidney to form VEM on anaerobic incubation in vitro. Although a detailed presentation of these latter aspects of the problem will be reserved for a subsequent paper, it seemed desirable to include some of the data here for the sake of completeness. A general discussion of the hepatorenal mechanisms regulating the metabolism of VDM and VEM is available for reference[1,2]; it should suffice for the interpretation of the data in this paper to point out that VEM and VDM are formed respectively by normal kidney and liver tissue under anaerobic and inactivated under aerobic conditions in vitro.

In order to evaluate the capacity of the liver to inactivate VDM under aerobic conditions, the liver slices were incubated with VDM obtained from either the liver wash or the plasma of animals in shock. Estimation of the inactivation capacity was based on a comparison of the original VDM content with the final VDM after the aerobic incubation and expressed as an inactivation index which was calculated as follows:

$$\frac{VDM_0 - VDM_f}{VDM_0} \times 100$$

For example, if a sample with a 20 minute VDM effect gave a neutral reaction after incubation with liver, the inactivation index of the liver would be 100. If there were a final VDM effect of 10 minutes, the index would be 50. An index of zero would indicate that no inactivation had taken place.

Experimental Results

The rat mesoappendix test was utilized for a comparison of the vasotropic activity of the blood and tissue extracts as well as for a correlation of *in vitro* and *in vivo* phenomena. Emphasis was placed not only on the sites of origin but also on the time of appearance of these vasotropic substances in the tissues in relation to the hyperreactive and hyporeactive phases of the shock syndrome. The complicated and time consuming nature of the experimental

procedures made it impossible to carry out bioassays on all the representative tissues for each animal. However, a sufficient number of assays were obtained with the different tissues to establish the presence or absence of these vasotropic principles in each phase of shock.

of the blood revealed the presence of VEM, the animals were sacrificed and various tissues assayed for their vasotropic content in the manner described above. Previous experience had shown that under these conditions animals exhibit the compensatory type of vascular

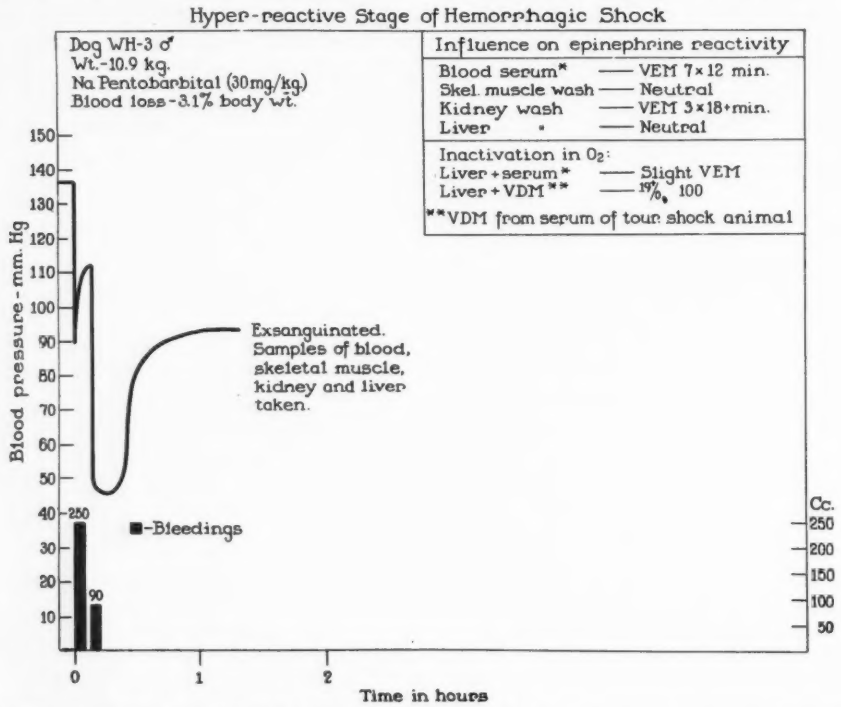

FIG. 4. Protocol of experiment 5 (table 1). Dog WH3 sacrificed in hyperreactive, reversible stage of hemorrhagic shock. Rat test data are in upper rectangle. In this and the following illustrations the data rela tn g to the inactivation index have been condensed in the following manner. The numerator gives the duration of the original VDM activity, the denominator the final VDM activity after aerobic incubation. The whole number is the inactivation index. See text for detailed description of the method of calculating the inactivation index.

A. *The Vasotropic Content of Various Tissues During Experimental Shock*

1. *Hemorrhagic Shock*

a. *The Initial Hyperreactive (Compensatory) Stage.* Eight dogs (experiments 1 to 8, table 1) were anesthetized with sodium pentobarbital and bled at intervals until the blood pressure remained between 60 to 75 mm. Hg in most instances and showed no tendency to rise. When this level of blood pressure had persisted for periods of 20 to 75 minutes and bioassays

hyperreactivity and are recoverable by blood replacement therapy.[22]

A protocol illustrating this type of experiment is given in figure 4 (experiment 5).

At 80 minutes following the initial hemorrhage when the blood pressure had stabilized at about 90 mm. (50 mm. below the control values) analysis of the blood serum revealed the presence of VEM, indicating the establishment of the hyperreactive compensatory phase. The renal cortex removed at this time contained VEM in comparable amounts to that present in the blood, as estimated from the fivefold dilution of the tissue content in the saline

wash. No difference could be detected in the responses of the vascular bed of the test rats to VEM from these two sources. Saline washes of the skeletal muscle and the liver were neutral. The capacity of the liver to inactivate VDM under aerobic conditions in vitro was well preserved (inactivation index = 100).

The composite picture of the tissue content of vasotropic factors in this group of animals was as follows.

Kidney: Kidney washes were examined in 5 animals in this group; all contained high concentrations of VEM as was apparent from the considerable activity manifested in the five-fold dilutions as compared to the undiluted plasma. The oxygen consumption of the kidneys removed from 3 dogs during this stage fell within the normal range (see table 4). Kidneys from 2 animals were examined for their capacity to form VEM on anaerobic incubation in vitro; this capacity was normally preserved in both.

Liver: In the 7 dogs in which liver washes were assayed, 6 gave neutral reactions and one a mild VDM effect. The livers were all pale and dry in contrast to the congested and wet state of the liver regularly observed during the decompensatory hyporeactive stage. Measurements of the rate of oxygen consumption of liver slices were made in 4 dogs during the hyperreactive stage; the values were in the upper range of normal (see table 4).

Skeletal Muscle: Skeletal muscle washes were examined in 3 of the animals; one gave a neutral reaction, the others contained moderate amounts of VEM, which, on the basis of in vitro incubation studies[1] is regarded as blood borne.

Cardiac and Smooth Muscle: In experiment 7 (dog D135) washes of cardiac and smooth muscle were neutral.

Spleen: Assays of the splenic washes of 3 animals gave varying results. In the first (experiment 3) the splenic wash was neutral; in the second (experiment 4) there was a very mild VDM response and in the third (experiment 7) the wash was grossly bloody and gave a moderate VEM response.

In one experiment (experiment 8, table 1) the plasma was incubated with normal kidney slices in oxygen to inactivate its VEM content. The bioassay after the incubation gave a neutral reaction indicating that the preponderance of VEM had not masked the presence of VDM.

These observations point to the kidney cortex as the tissue of origin of the blood-borne VEM present during the hyperreactive stage of hemorrhagic shock. They also demonstrate that there is no significant VDM formation in the liver during this phase of the shock syndrome. During this stage the over-all respiratory metabolism of the liver and kidney is not appreciably altered. The VDM inactivating mechanism of the liver and the capacity of the kidney to form VEM on anaerobic incubation in vitro are well preserved.

b. *The Hyporeactive (Decompensatory) Stage.* Inasmuch as our primary interest originally lay in the factors concerned with the development of irreversibility, the majority of experiments were designed to provide information as to the vasotropic content of the tissues during the hyporeactive (decompensatory or irreversibile) stage of hemorrhagic shock. This condition is regularly associated with the appearance of increasing amounts of VDM in the blood stream. Eighteen dogs (experiments 14 to 30, table 1) were subjected to graded hemorrhage under pentobarbital anesthesia. The initial bleedings were such as to reduce the blood pressure to levels of 70 to 90 mm. Hg and to sustain these levels for 90 to 120 minutes. Thereafter, the animals were maintained by further bleedings in extreme hypotension (usually below 45 mm. Hg) for periods of 40 to 190 minutes until significant amounts of VDM had appeared in the blood. In most experiments the blood pressure during the final 30 to 45 minutes was at 35 mm. Hg or below.

An example of this type of experiment is shown in figure 5 (experiment 19; see also table 1). Circulatory collapse ensued following the gradual withdrawal of blood equal to 5.6 per cent of the body weight and the maintenance of blood pressure below 45 mm. Hg for 90 minutes. Twenty-five minutes before death there was no response of the blood pressure to the reinfusion of 40 cc. of blood. At death, the blood serum showed a high concentration of VDM. Saline washes of the liver and skeletal muscle also contained VDM in considerable quan-

TABLE 1.—*Occurrence of VEM and VDM in Blood, Liver, Skeletal Muscle and Kidney during Hyper- and Hyporeactive Stages of Hemorrhagic Shock*

Procedure for induction of shock and preparation of tissues as described in section on methods. Reactivity of mesenteric blood vessels to epinephrine quantitated as follows:

VEM

0 = no change in reactivity
2×-30× = intensity of hyperreactivity, expressed as number of times control epinephrine solution was diluted at peak of hyperreactivity
min. = duration of hyperreactivity in minutes

VDM

0 = no change in reactivity
min. = duration of hyporeactivity, with complete loss of reactivity for one or more epinephrine applications unless designated as
mild = reactivity depressed but never completely lost

Experiment No.	Dog No.	Anesthetic Agent	Time from Initial Bleeding	Blood Pressure*	Influence on Epinephrine Reactivity			
					Plasma or serum	Liver wash (1:5)	Skeletal muscle wash (1:5)	Kidney wash (1:5)
Hyperreactive stage								
			Min.	*mm. Hg × Min.*				
1	D164	Pentobarbital	120	<80 × 75	VEM 4 × 32 min.	0		VEM 3 × 25 min. 1:10
2	D1	Pentobarbital	55	<70 × 25	VEM 10 × 16 min.	0		
3	D114	Pentobarbital	70	<70 × 20	VEM 6 × 29 min.	0		VEM 4 × 34 min.
4	D113	Pentobarbital	85	<70 × 50	VEM 4 × 27 min.	0		VEM 2 × 23 min.
5	WH3	Pentobarbital	80	<60 × 20	VEM 7 × 12 min.	0	0	VEM 3 × 18 min.
6	C22	Pentobarbital	75	<60 × 40	VEM 28 min.	0	VEM 15 min.	
7	D135	Pentobarbital	80	<60 × 75	VEM 3 × 21 min.		VEM 2 × 28 min.	
8	D157	Pentobarbital	90	<80 × 50	VEM 2 × 29 min.	VDM 15 min. mild		VEM 3 × 31 min.‡
9	WH13†	Pentobarbital	525	<45 × 130	VEM 3 × 7 min.	0		VEM 8 min.‡
10	C21	Cyclop.	185	<45 × 85	VEM 2 × 14 min.	mixed VDM + VEM	VEM 8	
11	C19	None	170	<45 × 95	VEM 5 ×	VEM 2 × 15 min.	VDM 14 min. mild	
12	WH8	None	215	<45 × 100	VEM 5 × 10 min.	VEM 4 × 8 min.	VDM 13 min. mild	VEM 30 ×
13	WH1	None	200	<45 × 115	0	VEM 3 × 15 min.	VDM 15 × min. mild	
Hyporeactive stage								
14	C8	Pentobarbital	120	<45 × 40	VDM 19 min.	VDM 17 min. mild		
15	WH11	Pentobarbital	220	<45 × 50	VDM 19 min.	VDM 22 min.		VEM 3 × 11 min.§
16	C12	Pentobarbital	180	<45 × 55	VDM 31 min.	VDM 23 min.		
17	D54	Pentobarbital	435	<45 × 60	VDM 15 min.	VDM 24 min.		
18	C11	Pentobarbital	160	<45 × 75	VDM 22 min.	VDM 20 min.		
19	C16	Pentobarbital	195	<45 × 90	VDM 28 min.	VDM 24 min.	VDM 19 min.	
20	D122	Pentobarbital	255	<45 × 110	VDM 24 min. 2:3	VDM 24 min. 1:10	VDM 20 min.	
21	C10	Pentobarbital	170	<45 × 110	VDM 25 min.	VDM 22 min.		
22	C17	Pentobarbital	190	<45 × 110	VDM 25 min.	VDM 23 min.	VDM 19 min.	
23	D3	Pentobarbital	300	<45 × 110	VDM 10 min.	VDM 13 min.		
24	D158	Pentobarbital	195	<45 × 120	VDM 33 min.	VDM 24 min.		VDM 2 × 20 min.§

25	D161	Pentobarbital	260	<45 × 125	VDM 20 min.	VDM 23 min.		VEM 1.3 × 16 min.‡
26	C7	Pentobarbital	325	<45 × 130	VDM 20 min.	VDM 24 min.		
2A	D1	Pentobarbital	310	<45 × 130	VDM 14 min.	VDM 22 min.		
27	C9	Pentobarbital	185	<45 × 135	VDM 31 min.	VDM 25 min.		VEM 4 × 11 min.
28	D57	Pentobarbital	335	<45 × 160	VDM 24 min.	VDM 21 min. mild		
29	D120	Pentobarbital	285	<45 × 170	VDM 18 min. 1:1	VDM 23 min. 1:10		0
30	C18	Pentobarbital	215	<45 × 190	VDM 26 min.		VDM 21 min.	
					Postinfusion-irreversible			
31	WH7	Pentobarbital	465	<45 × 90	VDM 22 min.	VDM 24 min.	VDM 15 min. mild	0
32	D121	Pentobarbital	205	<45 × 105	VDM 17 min. 2:3	VDM 26 min. 1:10		0§
33	WH9	Pentobarbital	450	<45 × 115	VDM 23 min.	VDM 20 min.	VEM 3 ×	VEM 2 × 8 min.§

* The figures in this column refer to the degree and duration of hypotension preliminary to the collection of the data except for experiments 9, 31, 32 and 33, in which the figures refer to the degree and duration of hypotension prior to reinfusion of blood.

† Exp. 9, Dog WH13, postinfusion, reversible.

‡ Anaerobic incubation of kidney Exp. 7 Dog D135 produced VEM 6 × 36 min.; Exp. 8 Dog D157 produced VEM 3 × 32 min.; Exp. 9, Dog WH13 produced VEM 10 × 18 min.; Exp. 25, Dog D161 produced VEM 2 × 18 min.

§ Exp. 24 Dog D158, Exp. 15 Dog WH11, Exp. 32 Dog D121 and Exp. 33 Dog WH9: subsequent incubation of kidney failed to produce VEM; apparently kidney after prolonged hypoxia had lost capacity to produce VEM.

TABLE 2.—*Occurrence of VEM and VDM in Blood, Liver, Skeletal Muscle and Kidney during Tourniquet Shock*

Procedure: Arterial tourniquets applied to both hind legs for 8 to 10 hours in the dog and for 4 to 6 hours in the rabbit except as otherwise noted in the table. Blood and tissues obtained when animals had gone into circulatory collapse except for studies on the hyperreactive phase which were terminated during the preponderance of VEM in blood. Blood and tissues prepared, assayed and VEM and VDM quantitated as in table 1.

Exp. No.	Animal No.	Anesthetic Agent	Tourniquets Applied for	Time after Tourniquet Release	Blood Pressure	Influence on Epinephrine Reactivity			
						Plasma	Liver Wash (1:5)	Tour. leg muscle wash (1:5)	Kidney wash (1:5)
						Hyperreactive stage			
			hours	*min.*	*mm. Hg-min.**				
34	Dog WH-5	Pentobarbital	3	60	<110 × 60	VEM 6 × 14 min.	0	VDM 15 min. mild	VEM 3 × 9 min.
35	Dog D163	Pentobarbital	3	125	<100 × 125	VEM 2 × 23 min.	0	VDM 27 min.	VEM 4 × 22 min.
36	Dog D149	Pentobarbital	3	100	<95 × 100	VEM 3 × 33 min.	0	0	VEM 3 × 24 min.
37	Dog D131	Pentobarbital	4	120	<80 × 120	VEM 3 × 20 min.	VDM 13 min. mild	VDM 24 min.	VEM 3 × 33 min.

Continued

TABLE 2. *Continued*

Exp. No.	Animal No.	Anesthetic Agent	Tourniquets Applied for	Time after Tourniquet Release	Blood Pressure	Influence on Epinephrine Reactivity			
						Plasma	Liver Wash (1:5)	Tour. leg muscle wash (1:5)	Kidney wash (1:5)
Hyporeactive stage									
			hours	*min.*	*mm. Hg-min.**				
38	Dog WH-2	Pentobarbital	8	135	<60 × 30	mixed VEM+VDM	VDM 26 min.	VDM 28 min.	VEM 6 × 11 min.
39	Dog WH-4	Pentobarbital	8	200	<60 × 55	mixed VEM+VDM	VDM 19 min.	VDM 25 min.	VEM 3 × 11 min.
40	Dog D162	Pentobarbital	9	225	<60 × 225	VDM 31 min. 1:1	VDM 36 min.	VDM 22 min. 1:30	VEM trace
41	Rbt L-9	Pentobarbital	5	45		VDM 33 min.	VDM 24 min.		
42	Rbt WH-9	Pentobarbital	5	55		VDM 19 min.	VDM 18 min.		VEM 2 × 7 min.
43	Rbt CR-9	Pentobarbital	4	82		VDM 23 min.	VDM 19 min.		VEM 6 × 20 min.
44	Rbt L-19	Pentobarbital	4	90		VDM 28 min.	VDM 20 min.		
45	Rbt WH-6	Pentobarbital	6	120		VDM 19 min. mild	VDM 19 min. 1:10		VEM 3 ×
46	Rbt 6-11	Pentobarbital	5	130		VDM 27 min.	VDM 25 min.		
Tourniquet limbs taped (D-12–D-32) or encased in plaster (D-35)									
47	Dog D-32	Seconal	10	290	<60 × 75	VDM 19 min.	VDM 26 min.	VDM 21 min.	0
48	Dog D-35	Seconal	10	10	<80 × 5	mixed VEM+VDM			
			10	40	<110 × 40	VEM 2-12 min.			
			10	75	<90 × 5	VDM trace or 0	VDM 25 min. 1:10		
			10	180	<90 × 105	VDM 30+min.			
			10	300	<60 × 5	VDM 20 min.	VDM 30 min.		VDM 16 min.
49	Dog D-12	Seconal	10	75	<140 × 75	0			
			10	185	<90 × 95	VEM 2 × 15 min.			
			10	320	<60 × 55	VDM 18 min.	VDM 18 min.	VDM 33+min.	VEM 2 × 18 min.
Bioassays of muscle carried out 3 to 9 hours after application of tourniquet and just prior to its release									
50	Dog WH18	Pentobarbital	5					VDM 19 min.	
51	Dog C-15	Pentobarbital	5					VDM 28 min.	
52	Dog C-20	Pentobarbital	5½					VDM 26 min.	
53	Dog D153	Pentobarbital	3					VDM trace	
		Pentobarbital	6					VDM 19 min. mild 1:15	
		Pentobarbital	9					VDM 36 min. 1:15	

* The figures in this column indicate the degree and duration of hypotension preliminary to the collection of the data.

tities, the concentration being greater in the liver wash. The amount of VDM in the liver wash, which represented a 1 to 5 dilution with saline, was comparable to that in the undiluted serum. The washes of cardiac and smooth muscle were neutral, that from the spleen contained moderate amounts of VEM.

A comparison was made of the capacity of this liver and the liver from a normal control to inactivate, during a two hour aerobic incubation in vitro, the VDM present in the blood serum obtained at death. The inactivation index of normal liver slices was 72; that of the liver of the shocked animal was 33.

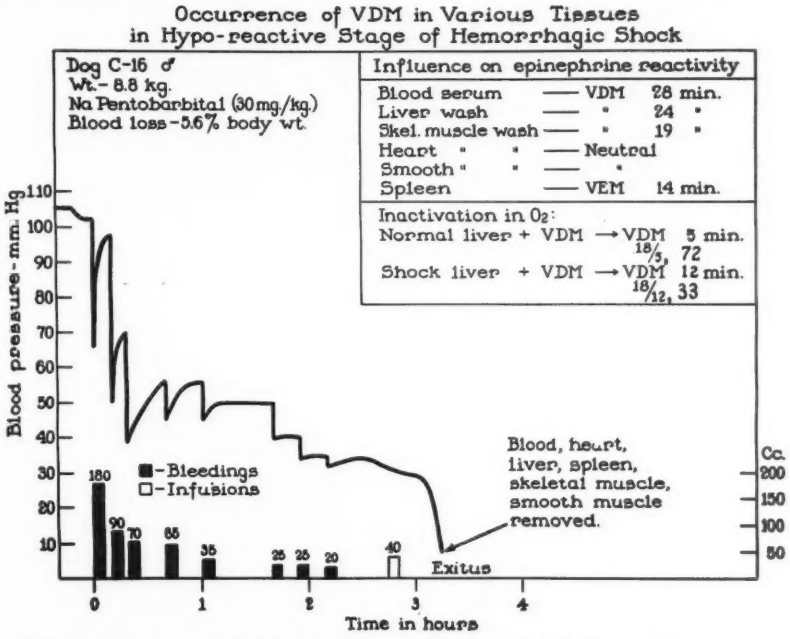

FIG. 5. Protocol of experiment 19 (table 1), dog C16. It illustrates findings in hyporeactive irreversible stage of hemorrhagic shock. Comparative studies were made, utilizing the same VDM sample, of VDM inactivation capacity of liver from animal in shock and from a normal control.

A summary of the tissue assays is as follows:

Liver: In 17 of the 18 animals, liver washes were assayed and all showed VDM. In most instances, the concentrations were equal to those in the blood despite the usual fivefold and occasional tenfold dilution represented by the liver wash. Comparisons of the VDM titers of hepatic vein and peripheral blood in 4 dogs (experiments 14, 21, 26 and 27) showed no significant differences. The livers removed during the hyporeactive stage were typically congested and moist. The average oxygen consumption of 18 such livers was 85 per cent of the normal (see table 4). The VDM inactivation capacity of the liver from 15 dogs in the hyporeactive stage was found to be disproportionately depressed, the average inactivation index being 18.

Skeletal muscle washes were analyzed in four experiments; VDM was present in all.

Cardiac and Smooth Muscle: In two experiments (experiments 19 and 20) saline washes were prepared from cardiac and smooth muscle. These were devoid of vasotropic activity.

Kidney: Of five kidney washes, three showed moderate concentrations of VEM, one a small amount, and the fifth was neutral. These concentrations of VEM were lower than in saline washes of kidneys removed during the hyperreactive stage. The significance of this last finding will be discussed in the following section of this paper. Measurements of the oxygen consumption of the kidneys were made

in 4 dogs and were found to be within the normal range (see table 4).

Spleen: In the experiments in table 1, both of the hyper- and the hyporeactive types, the assays of splenic washes gave the variable results noted above. They were sometimes neutral and in other instances contained small amounts of VEM or VDM which we regarded as originating in the blood retained within the spleen. Later studies with highly concentrated VDM solutions prepared in this laboratory by Dr. A. Mazur showed that very high concentrations of VDM sometimes yielded systemic vascular effects which interfered with the interpretation of the purely peripheral effects on the arterioles and precapillaries; however, typical VDM responses could be obtained with these concentrates by appropriate dilution. A similar phenomenon was observed with highly concentrated VEM solutions prepared by Dr. R. F. Furchgott. These observations led to the re-examination of the saline washes of the various tissues in shock to determine whether the presence of VEM or VDM under our experimental conditions might have been masked in the rat test by excessive concentrations of these vasotropic principles. In only one organ, the spleen, was this found to be the case. Six dogs were allowed to go into hyporeactive hemorrhagic shock and splenic washes made in varying dilutions. In each instance saline dilutions of 1 to 50 instead of the conventional 1 to 5 elicited moderate to marked VDM responses in the mesoappendix test.

Although it was felt that the contribution of splenic VDM to the development of hyporeactivity was of little significance, in view of the abundant evidence of its markedly contracted state throughout and hence its virtual exclusion from the circulation,[23] more direct evidence for this inference was provided by an experiment in which hemorrhagic shock was induced in a splenectomized dog. Graded hemorrhage, with the withdrawal of blood equal to 4.7 per cent of body weight, led to the typical blood pressure changes previously described and to the sequence of humoral and tissue vasotropic events characteristic of animals with intact spleens.

These findings as to the vasotropic content of the tissues in the hyporeactive stage of hemorrhagic shock may be summarized as follows. VDM has its origin in liver, spleen and skeletal muscle. The concentrations in the liver, as determined in fivefold dilutions, appear to be as great as and are probably greater than the concentrations in plasma which was assayed in undiluted form. Although there is only a slight reduction in over-all oxygen consumption, the VDM inactivation mechanism of the liver is profoundly impaired. The concentrations of VEM in the kidney wash are lower than during the hyperreactive phase, and the ability of the kidney to form VEM on anaerobic incubation may be lost; however, the oxygen consumption of the kidney is still in the normal range.

c. *Hyporeactive Shock Studied after Blood Replacement.* In the previous section it was pointed out that the amount of VEM in the kidney wash during the hyporeactive phase of hemorrhagic shock was generally less than that observed during the hyperreactive phase; indeed, in experiment 29, dog D120 (table 1) in which the period of hypotension (less than 45 mm. Hg) lasted 170 minutes, VEM was absent from the wash. Furthermore, in contrast to kidneys removed during the hyperreactive stage, the kidneys of 2 of 3 dogs studied during the hyporeactive phase had lost the ability to form VEM on anaerobic incubation in vitro. This suggested that the renal hypoxia resulting from hypotension might have been responsible for the impairment of the renal mechanisms for the formation of VEM. This observation was amplified by four additional experiments in which, following the usual period of drastic hypotension, the blood lost was reinfused to test the effect of this procedure on the renal VEM mechanisms (experiments 9, 31, 32 and 33, table 1).

A protocol of such an experiment is given in figure 6. Hemorrhagic shock was induced under pentobarbital anesthesia in experiment 32, dog D121, by graded hemorrhage with the removal of 4.4 per cent of the body weight. The initial period of moderate hypotension (about 60 mm. Hg) was of 70 minutes duration. Thereafter the blood pressure fluctuated around 40 mm. Hg for 105 minutes, during the last 45 minutes of which the animal was

supported with three infusions totaling 360 cc. This resulted in a brief rise in blood pressure to 60 mm. of Hg, followed by a rapid circulatory collapse three and one-half hours after the initial bleeding. Bioassays of the blood samples showed a neutral reaction prior to bleeding; the presence of very considerable VEM activity 50 minutes after the initial bleeding; and VDM 20 minutes prior to death. Incubation of this last blood sample with antiserum to ferritin[24] (with which VDM has been identified[25]) abolished the VDM activity, leaving a neutral reaction indicative of the absence of VEM. The liver wash in a 1:10 dilution contained even larger amounts of VDM than did the blood. This liver proved unable to remove the VDM from plasma sample 3 with which it was incubated under aerobic conditions. The oxygen consumption of the liver was 0.67 cc. per Gm. wet weight per hour which was within the normal range although below the normal average of 0.74. The findings with kidney were of particular interest. The oxygen consumption of the renal cortex was 2.27, well within the normal range. The kidney wash, however, contained no VEM, nor did the kidney form VEM on anaerobic incubation in vitro. This animal thus exhibited two metabolic defects related to the hepato-renal vasotropic factors. The liver had lost the capacity to inactivate VDM aerobically and the kidney to form VEM under anaerobic conditions. Both defects existed despite the retention of normal over-all oxidative capacity on the part of both organs. Analysis of the blood prior to death showed that the VEM formerly present had disappeared completely.

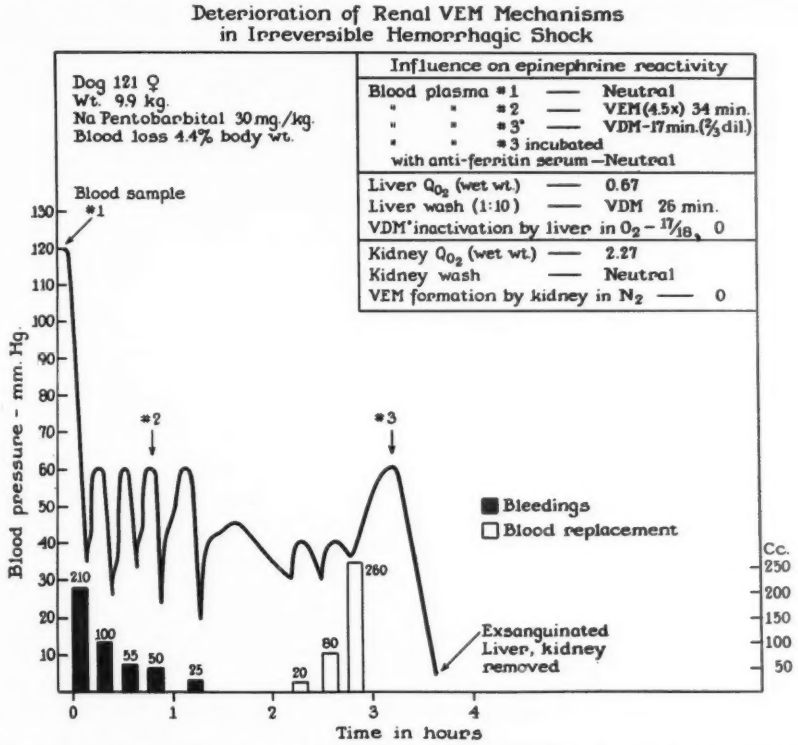

FIG. 6. Protocol of experiment 32 (table 1), dog 121. It illustrates deterioration of renal VEM mechanisms during hyporeactive phase of irreversible hemorrhagic shock. Prolongation of hyporeactive phase by blood replacement served to delay onset of circulatory collapse. At death there was deterioration not only of VDM inactivation capacity, but also loss of renal capacity to form VEM. Note disappearance of VEM from blood in sample 3.

Two of the remaining 3 animals died in circulatory collapse within two to three hours after blood replacement therapy. One dog (experiment 9) recovered and was sacrificed four hours after the reinfusion, at which time there was a moderate concentration of VEM in the plasma and the kidney wash; the saline

wash of the liver was neutral; and the kidney was found capable of forming normal amounts of VEM on anaerobic incubation in vitro. This was in sharp contrast with the findings in the 3 animals which proved irreversible; in all 3, VDM activity persisted in the blood despite the reinfusion and the temporary rise in blood pressure. The livers were found to be highly congested at death and to contain considerable amounts of VDM. The kidney wash of only one of these animals (experiment 33) exhibited VEM activity and this was of a mild degree. This kidney, as well as the kidney in experiment 32, failed to produce any VEM on subsequent anaerobic incubation.

Evidently prolonged hypotension, sufficient to produce hyporeactive shock, not only initiates VDM formation and adversely affects the hepatic VDM inactivation mechanism but also impairs the capacity of the kidney to form VEM, presumably through renal hypoxia.

d. *Relation of Anesthesia to Formation of VDM.* One difference between experiments dealing with the hyporeactive type of shock and those which were interrupted during the hyperreactive phase is the shorter period (55 to 120 minutes) between the initial bleeding and the removal of tissues for study in the latter experiments. The absence of VDM from the wash of liver obtained during the hyperreactive phase might conceivably have been due to the briefer duration of the period of hypotension. To clarify this point, advantage was taken of the difference in the response of anesthetized and unanesthetized dogs to graded hemorrhage. Following a period of hypotension which, in dogs under *pentobarbital anesthesia*, is sufficiently prolonged and drastic to produce uniformly hyporeactivity, VDM formation in the liver, and irreversibility, *unanesthetized* animals remain in the hyperreactive, compensatory stage until death and are recoverable by transfusion.

Three unanesthetized dogs (experiments 11 to 13, table 1) were bled so as to achieve the same degree and duration of hypotension which had uniformly produced hyporeactivity and VDM formation in the liver in dogs subjected to hemorrhage under pentobarbital anesthesia. The arterial cannula for recording blood pressure was introduced into the femoral artery under procaine anesthesia.

Figure 7 (experiment 12, dog WH8) provides an example of the response of the unanesthetized dog to graded hemorrhage with the removal of 4.7 per cent of body weight of blood. Circulatory failure developed 215 minutes after the initial bleeding and following a period of hypotension below 45 mm. Hg for 100 minutes. A blood sample taken at this time showed VEM in contrast to the VDM usually found in anesthetized dogs following an equivalent period of hypotension. The liver wash at this stage was completely free of VDM activity. Skeletal muscle had only small amounts of VDM. The kidney contained unusually large amounts of VEM, the wash producing in the test rat a thirtyfold increase in the reactivity to epinephrine. The oxygen consumption of the liver was in the normal range. The liver capacity for inactivation of VDM was unimpaired.

In the other two dogs of this group (experiments 11 and 13) VEM was present in the blood of one at death; the blood of the other gave a neutral reaction. Liver washes of both animals were devoid of VDM; instead they manifested vasoexcitor activity, presumed to be blood borne. VDM of mild activity was present in the skeletal muscle wash. The livers of all three of these animals were firm and pale and bled only slightly when incised, in contrast to the friable engorged livers of anesthetized dogs with the same degree and duration of hemorrhagic hypotension.

The formation of VDM by the liver, therefore, does not appear to be specifically dependent on the *duration* or *degree* of the hypotension, per se. The circumstance responsible for the inauguration of VDM formation by the liver would appear, from in vitro and in vivo experiments, to be the extent to which hypotension leads to liver hypoxia during the shock syndrome. The evidence for this conclusion will be given in detail in a subsequent paper dealing with the mode of origin of VDM and VEM.

In this connection the findings in animals bled under cyclopropane anesthesia are of interest since shock under these conditions represents a state intermediate between the hyperreactive type of shock characteristic of unanesthetized animals and the hyporeactive type manifested by animals under pentobarbital anesthesia. The essential findings in

one such experiment (experiment 10, table 1) were as follows: Cyclopropane was administered intermittently with oxygen (75 to 90 per cent), using a closed to and fro rebreathing system and a canister for carbon dioxide absorption. The uppermost (first) plane of surgical anesthesia was maintained throughout.* Graded hemorrhage to a total of 3.9 per cent of the body weight led to a fall of blood pressure from 158 mm. Hg to between 50 and 60 mm. in 45 minutes. When this period of hypotension had lasted 60 minutes, the withdrawal of additional blood to a total of 4.4 per cent of the body weight led to a further fall in blood pressure which remained between 30 and 40 mm. for 85 minutes at which time the animal was exsanguinated and tissue samples obtained. The blood withdrawn at that time gave a mild VEM effect in the test rat. The liver wash contained small amounts of both VDM and VEM. These findings indicate that the animal was in a stage transitional to the disappearance of VEM from the blood stream and its replacement by VDM. The wash of skeletal muscle obtained simultaneously with the liver and blood sample showed considerable VEM activity, presumably blood borne and suggestive of the persistence of an adequate blood flow through the muscle during the shock stage. The oxygen consumption of the liver remained within the normal range.

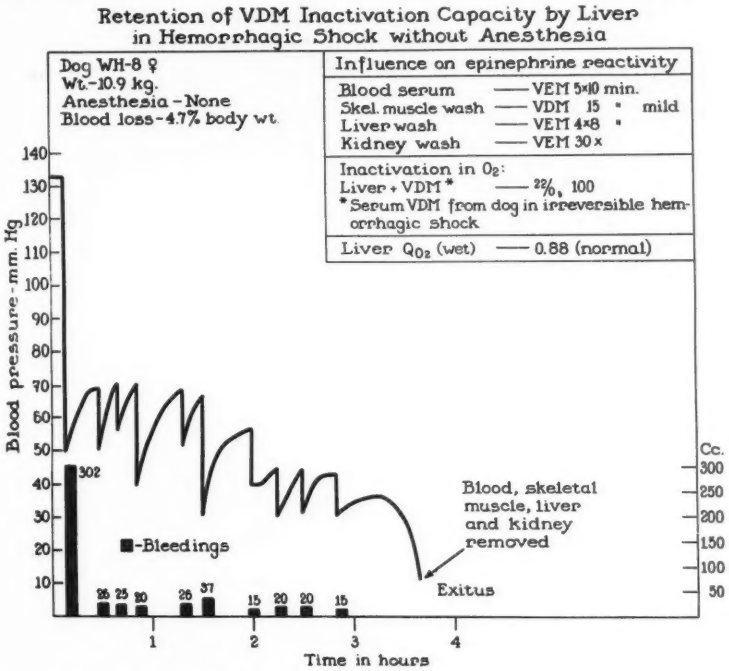

FIG. 7. Protocol of experiment 12 (table 1). Dog WH8 subjected to graded hemorrhage without anesthesia.

e. *Serial Liver Biopsies during the Evolution of the Shock Syndrome.* In order to ascertain more precisely the time relationships between the development of hyper- and hyporeactivity as determined by the bioassay of the blood for VEM and VDM, and the onset of VDM formation by the liver, the following experiment was carried out. Hemorrhagic shock was induced in a dog by graded hemorrhage under sodium pentobarbital anesthesia. Serial bioassays were made of the blood and of the washes of liver biopsies obtained simultane-

*The anesthesia was administered by Dr. S. G. Hershey, Department of Anesthesia, New York University College of Medicine.

ously during the progression of the shock syndrome through the hyper- and hyporeactive phases.

The data from this experiment (experiments 2 and 2A, table 1) have been assembled in figure 8. The control liver biopsy and blood sample taken prior to the bleeding gave neutral reactions in the rat test. Fifty-five minutes after the first bleeding, when the animal's blood pressure had been at a level of about 70 mm. for 25 minutes, the hyperreactive stage had set in, as evidenced by the presence of considerable amounts of VEM in the blood. However, the liver biopsy taken at the same time gave a neutral reaction. The third blood sample was removed about 4 hours after the initial bleeding and following a period of 100 minutes in which the blood pressure ranged between 40 and 50 mm. Hg. This blood gave a neutral reaction in the test rat indicating that the animal was in a stage transitional between the hyper- and hyporeactive phases and characterized by a gradual disappearance of vascular hyperreactivity. This transitional phase may be indicative either of the disappearance of VEM or, more probably, of a waning effectiveness of VEM due to its being masked by equivalent concentrations of VDM. Bioassay of the corresponding liver biopsy supported the latter possibility since it showed that VDM formation in the liver had already begun. The last samples were taken when the animal was in obvious circulatory failure. The blood now contained VDM in amounts usually found during the hyporeactive phase and the liver wash showed a slightly greater concentration of VDM than in the previous liver biopsy. The concentration of VDM in the liver wash, despite the fivefold dilution with saline, was greater than in the undiluted blood plasma. Studies were also made of the efficiency of the VDM inactivation mechanism in liver during the progression of the shock syndrome, utilizing tissue slices from the liver biopsies. During the hyperreactive stage when VDM formation was absent there was only a slight reduction in this capacity. Thereafter a progressive impairment of this mechanism was observed.

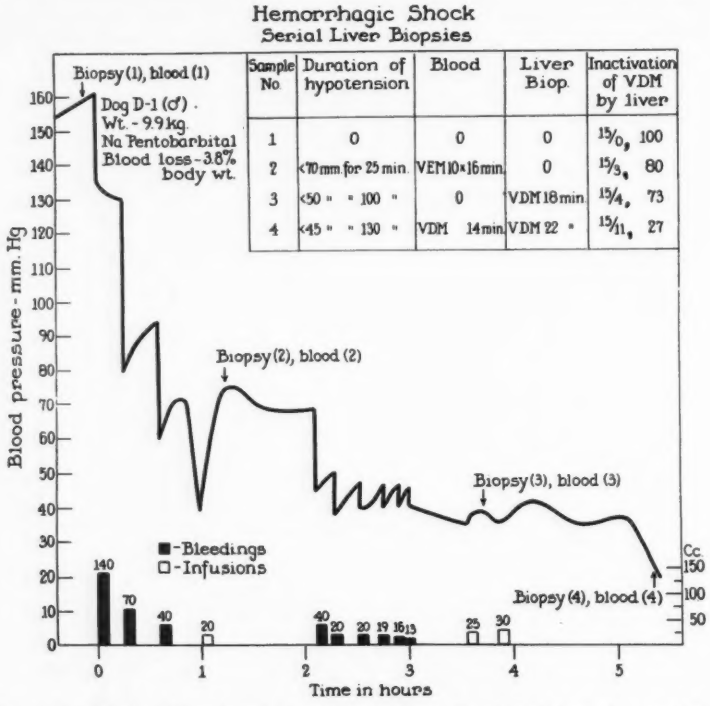

FIG. 8. Protocol of Experiment 2 and 2A (table 1). Dog Dl subjected to graded hemorrhage with several liver biopsies taken during syndrome.

This experiment provides additional evidence that no VDM formation takes place during the hyperreactive phase of hemorrhagic shock, that VDM is present in the liver prior to its appearance in the blood and that the concen-

trations in the liver are greater than in the blood taken simultaneously. It also demonstrates that the liver sustains a progressive impairment of its VDM inactivating mechanism during the hyporeactive stage of the syndrome. The regularity with which this deterioration occurs is evident from figure 9, which summarizes our data on the liver inactivation mechanism in normal animals and in the hyper- and hyporeactive stages of experimental shock.

Evidence of another type was provided as to the sequence of humoral vasotropic events during the evolution of the shock syndrome. Hemorrhagic shock was produced in dog 186 (not included in the tables) and blood removed for bioassay during the hyperreactive, transitional and hyporeactive stages of the syndrome. The blood during the hyperreactive stage contained high concentrations of VEM. In the transitional stage an essentially neutral reaction was obtained. This blood sample was then fractionated in two ways: VEM was inactivated by aerobic incubation with normal kidney slices; VDM was inactivated by incubation with antiserum to VDM[24] (ferritin).[25] Bioassays after these procedures showed that moderate and approximately equal amounts of both VEM and VDM were present. During the hyporeactive stage the untreated plasma gave a strong VDM test. Following the same fractionation procedures, the amount of VDM was practically unchanged and no VEM could be detected. Evidently, at the transitional period the neutral reaction was a resultant of a balance between the waning concentrations of VEM and the newly present VDM; thereafter, with the progression of the syndrome, there was a progressive reduction and eventual disappearance of humoral VEM.

2. *Tourniquet Shock*

Previous experiments[18] have shown that in tourniquet shock, as in the hemorrhagic, the syndrome consists of two stages, an initial hyperreactive compensatory and a subsequent hyporeactive or decompensatory phase. Both the intensity and duration of the vascular response can be modified in a predictable manner by varying specific experimental conditions. For example, a predominantly hyperreactive response terminating in vascular collapse accompanied by pronounced vasoconstriction may be obtained in dogs by applying venous tourniquets to all four limbs or arterial tourniquets to two limbs for a relatively short period of time (four to five hours). Under these conditions the syndrome is primarily the result of the local accumulation in the injured limbs of sufficient fluid to induce collapse. The peripheral vascular symptoms are identical with those which accompany simple massive hemorrhage. It is of interest

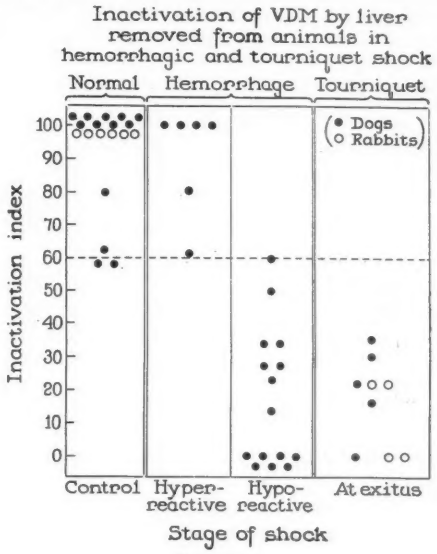

FIGURE 9

that such animals are readily recoverable by fluid replacement therapy. On the other hand, a predominantly decompensatory type of response terminating in circulatory collapse with vascular hyporeactivity may be induced by applying arterial tourniquets to two limbs for eight to ten hours. Transfusion therapy is usually unsuccessful in such animals. A response intermediate between these two extremes, with an initial hyperreactivity of variable duration followed by hyporeactivity, may be induced by applying arterial tourniquets to two limbs for six to seven hours.

Two types of experiments are reported here. In one group of dogs the hyperreactive phase

was emphasized by applying arterial tourniquets to two limbs for three to four hours and interrupting the syndrome when VEM was found to be present in the blood. In another series of animals the hyporeactive phase was achieved by applying tourniquets to the hind limbs for eight to ten hours in dogs and for four to six hours in rabbits.

The data for the present experiments on tourniquet shock in dogs and rabbits are assembled in table 2. An important difference between hemorrhagic and tourniquet shock is the formation of considerable amounts of VDM by skeletal muscle during the application of the tourniquets (experiments 50, 51, 52 and 53, table 2) and its discharge into the circulation upon the release of these ties. The promptness with which this discharge of VDM occurs is especially shown in experiments in which the kidney was occluded prior to the release of the tourniquets (experiments 62 and 63, table 3). It is evident from experiment 53 (table 2) that the amount of VDM formed is conditioned by the period over which the tourniquets have been applied. As a consequence, during the initial phase of tourniquet shock there is a variable admixture in the peripheral circulation of skeletal muscle VDM and of VEM of renal origin. This parallel contribution of VDM influences the extent and duration of the predominance of VEM and of its associated hyperreactivity.

The findings as to the vasotropic content of blood and tissues during these two phases of tourniquet shock were essentially similar to those described above for hemorrhagic shock.

a. *The Hyperreactive Phase.* Four dogs (experiments 34 to 37, table 2) with tourniquets applied for three to four hours are included in this category on the basis of the VEM activity of the plasma samples. In all four instances the kidney washes showed considerable VEM activity. Bioassays of the muscle washes from the tourniqueted limbs gave variable results; one was neutral, another gave a mild VDM reaction and the remaining two washes gave strong VDM assays. The liver wash gave a neutral reaction in 3 of the animals; in the fourth there was a mild VDM reaction. The presence of these small amounts of VDM in the liver of this animal at a time when VEM was predominant in the blood suggests either that the liver was accumulating skeletal muscle VDM from the blood or that the dog was undergoing a transition from the hyper- into the hyporeactive stage with the initiation of VDM formation in the liver. (See figure 8 in which serial liver biopsies reveal the presence of VDM in liver prior to its demonstration in the blood stream; also experiments 8 and 10, table 1).

b. *The Hyporeactive Phase.* In this group are included experiments on 3 dogs and 6 rabbits in which tissue and blood assays were made when the animals were in obvious circulatory collapse (experiments 38 to 46, table 2). In 2 dogs (experiments 38 and 39) bioassay of the plasma showed a mixture of VEM and VDM effects; in all other animals VDM predominated. Large amounts of VDM were present in the washes of the livers of all 9 animals sacrificed during the hyporeactive stage of tourniquet shock. The livers of 9 such animals were also examined for their oxygen consumption. The results were in agreement with the findings on the livers of dogs in the hyporeactive stage of hemorrhagic shock. The average oxygen consumption for the livers of 6 shocked dogs was 88 per cent of the normal; for 3 shocked rabbits, however, it was unimpaired (table 4). The capacity of the VDM inactivation mechanism had fallen profoundly; in 5 dogs to an average index of 21, in 4 rabbits to an average index of 11 (compared with an index of 80 to 100 in controls). Washes of the renal cortex obtained in 6 animals uniformly exhibited VEM activity. Saline washes of the tourniqueted limb muscles of 3 dogs manifested very considerable VDM activity.

A representative protocol of the findings in hyporeactive tourniquet shock (experiment 38, table 2) is given in figure 10. The blood at death contained a mixture of VEM and VDM, the latter predominating. The saline wash of the liver, despite a 1:5 dilution, exhibited even greater VDM activity. In addition the VDM inactivating capacity of the liver was completely lost. There was a high content of VDM in the wash of skeletal muscle. The kidney wash exhibited VEM activity. Saline washes of cardiac and smooth muscle were neutral.

Splenic wash in a 1 to 5 dilution was also neutral; however, no tests were made with greater dilutions.

c. *Tourniquet Shock in Animals in Which the Tourniqueted Limbs Were Taped or Encased in Plaster.* In these experiments, the local swelling which occurs after release of the tourniquets was restricted by taping the limbs or encasing them in plaster before the tourniquets were applied. Previous studies[18] had demonstrated that when the limbs were taped and tourniquets released after six to seven hours, 3 out of 7 animals recovered, whereas under similar conditions all untaped animals died. However, when the tourniquets were applied for 10 hours, their release was followed by shock which terminated in circulatory collapse despite taping. The shock syndrome under these experimental conditions cannot be attributed to a reduction in blood volume through its loss into the tourniqueted limbs and hence constitutes a state for which the fluid-loss concept provides no explanation.

The present experiments (experiments 47 to 49, table 2) were carried out with a view to a more exact analysis of the sequence of humoral and tissue events associated with this type of shock. In two of the dogs the limbs were tightly taped, in the third they were encased in plaster. The tourniquets were then applied for 10 hours.

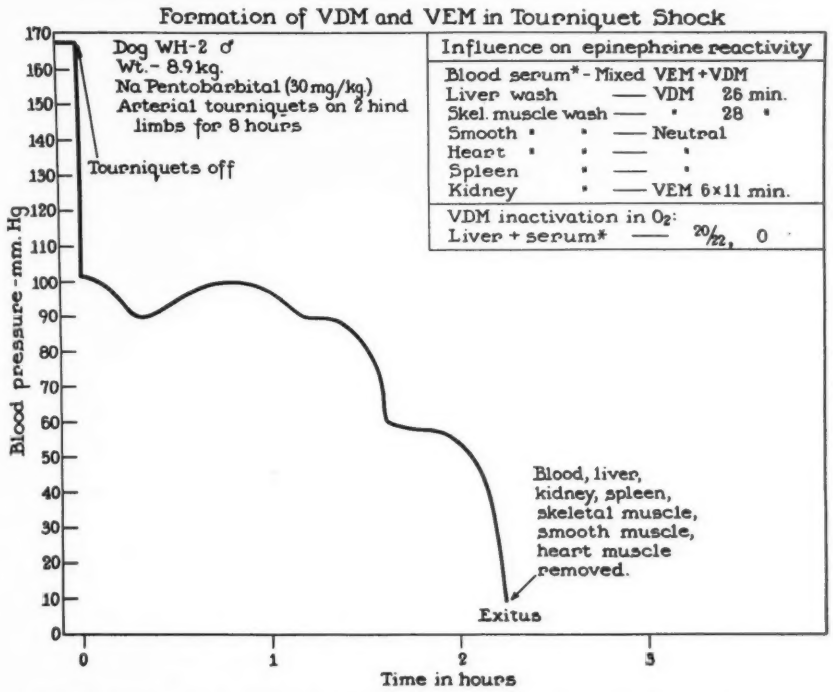

FIG. 10. Protocol of experiment 38 (table 2). Dog WH2 subjected to tourniquet shock.

A protocol of experiment 48 is illustrated in figure 11. The details of the anesthesia and the method of inducing shock are given in the figure. A catheter was inserted into the inferior vena cava via the jugular vein to permit analysis of the blood coming exclusively from the previously tourniqueted limbs. Mixed peripheral blood was obtained from the jugular vein. Immediately on release of the tourniquets there was a profound and sharp fall in blood pressure followed by a prompt rebound to somewhat higher levels. From previous studies,[26] it would appear that nonspecific vasodilator substances resulting from the deterioration of the skeletal muscles contribute in considerable measure to this initial sharp fall in blood pressure. In the present experiments successive blood samples obtained from the inferior vena cava contained large amounts of VDM

throughout the syndrome. Despite the continued introduction of skeletal muscle VDM, analysis of the mixed peripheral venous blood showed a brief predominance of VEM activity. However, at 75 minutes the peripheral blood had reverted to a neutral state, indicative of neutralization by VDM of the VEM present; thereafter VDM predominated. A liver biopsy obtained 75 minutes after the release of the tourniquets revealed a high concentration of VDM, but the VDM inactivation capacity was unimpaired. The oxygen consumption of the

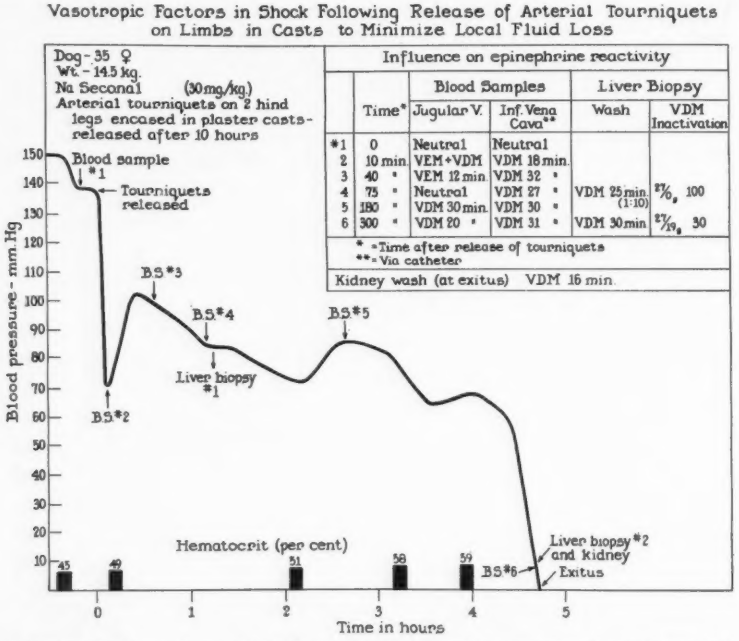

FIG. 11. Protocol of experiment 48 (table 2). Dog D35 in which tourniquet shock was induced with hind limbs encased in plaster casts. No swelling of injured limbs was noted at death. Separate analyses of mixed peripheral venous blood and that coming from previously tourniqueted limbs was made possible by a catheter in inferior vena cava below renal veins.

liver was also normal. The VDM content of the liver wash at this time is regarded as chiefly blood-borne skeletal muscle VDM, since the degree and duration of hepatic hypoxia which would be required to form this amount of VDM invariably leads to a marked impairment of the VDM inactivation mechanism. The liver biopsy obtained at death three and three-quarter hours later showed large amounts of VDM along with a decrease in the VDM inactivation index of the liver to 30 as compared with 100 in the first liver biopsy. The VDM activity in this liver wash is regarded as being the result of both blood-borne skeletal muscle VDM and hepatic VDM resulting from local liver hypoxia, the latter inference being supported by the deterioration of the VDM inactivation mechanism. Hematocrit determinations were carried out at intervals throughout the syndrome. A slight hemoconcentration occurred during the first two and one-half hours after the release of the tourniquets; thereafter the hemoconcentration was more pronounced. The kidney wash obtained at death showed, instead of VEM, very appreciable amounts of VDM, believed to be a reflection of the large amounts of VDM in the circulation. The liver and abdominal viscera were characteristically congested and the tourniqueted limbs were without evidence of edema. Particularly noteworthy was the marked congestion of the kidneys.

The remaining two animals in this group (experiments 47 and 49, table 2) showed essentially the same picture. Each exhibited the initial sharp fall in blood pressure noted above, followed by a transient rise and subsequent steplike reduction with progressive hypotension and circulatory collapse. The sequence of humoral events is shown in table 2. In each animal hyporeactivity developed as indicated by the humoral predominance of VDM. High concentrations of VDM were

present in the liver wash, the concentrations being greater than in the parallel blood samples in view of the fivefold dilution of the liver wash. The VDM inactivation index of the liver of the dog in experiment 47 had fallen to 35, in experiment 49 this index had fallen to 17; the oxygen consumptions of both were still within the normal range. At death skeletal muscles from these animals contained high concentrations of VDM. The oxygen uptake of these muscles was zero. As in the arenal animals, to be described below, accentuation of the vascular decompensatory aspects of the syndrome was indicated by the marked splanchnic congestion at autopsy, particularly of the liver, kidney and intestinal tract. In neither animal was there appreciable swelling of the tourniqueted limbs.

These experiments help to clarify the initiation and evolution of the syndrome of tourniquet shock. The initial brief period of drastic hypotension is believed to be due to the release of nonspecific breakdown products of muscle origin and to the sudden diminution of peripheral resistance due to the opening up of the circulation in the previously occluded limbs. Thereafter, large amounts of VDM are continuously released from the injured limbs in concentrations sufficient to overwhelm the renal VEM contribution, gain rapid predominance in the blood stream and initiate the type of vascular hyporeactivity which is invariably associated with peripheral circulatory collapse. This inference is buttressed by previous experiments[18] in which direct visualization of the omental bed during the progression of this type of tourniquet shock revealed a mild initial vascular hyperreactivity, followed by the decompensatory hyporeactivity regularly associated with the predominance of VDM in the blood stream. During the latter part of the syndrome both hepatic and skeletal muscle VDM contribute to accentuate the vascular decompensatory reactions. In the early stage of the syndrome, it is believed that the liver collects large amounts of VDM of skeletal muscle origin. Thereafter, with the persistence and progression of the hypotension, liver hypoxia presumably ensues, anaerobic processes are initiated with the local formation of VDM and progressive deterioration of the hepatic VDM inactivation mechanism. In summary, these data are regarded as suggestive of a causal relationship between VDM and the vascular decompensatory behavior associated with peripheral vascular collapse in these animals.

B. *The Relation of the Renal VEM Mechanism to the Hyperreactive Stage of Shock*

Although the previous experiments appeared to establish the exclusive origin of VEM in the kidney it seemed desirable to provide additional evidence for this conclusion by excluding the kidney from participation in the shock syndrome and observing the manner in which this procedure might modify the sequence of humoral and tissue vasotropic phenomena previously observed.

1. *Hemorrhagic Shock following Renal Occlusion.* Four experiments (experiments 54 to 57, table 3) of this type were carried out under sodium pentobarbital anesthesia. In all, the hyperreactive stage failed to develop as evidenced by the absence of VEM in the blood at any time in the syndrome. At least one blood sample was obtained from each of the dogs at a time following the initial hemorrhage when VEM was invariably present in dogs with intact kidneys. In 3 of the 4 animals VDM appeared in the blood with unusual rapidity. In 3 dogs (experiments 54, 55 and 57) profound hypotension (below 45 mm. Hg) was achieved with the removal of blood equivalent to only 2.8 per cent, 3.0 per cent and 3.2 per cent of the body weight. This degree of hypotension set in with unusual rapidity; in dog D156, 50 minutes, in dog D100, 30 minutes, and in dog D167, 25 minutes after the initial bleeding. These 3 dogs were reinfused with all the blood removed and proved irreversible.

A representative protocol is given in figure 12 (experiment 56, dog D2). The renal circulation was bilaterally occluded by the application of ties about 35 minutes before bleeding was initiated. A blood sample taken 45 minutes after the initial bleeding, at a time when VEM is regularly present in animals with intact kidneys, gave a neutral reaction. The next blood sample taken 60 minutes later exhibited mild VDM activity indicative of the early initiation

TABLE 3.—*Effect of Renal Occlusion on the Vasotropic Content of Blood in Hemorrhagic and Tourniquet Shock*

Procedure for induction of shock and preparation of tissues as described in section on methods. Reactivity of mesenteric blood vessels to epinephrine quantitated as in table I.

Exp. No.	Dog No.	Operative Preparation Time before bleeding in parenthesis	Anesthetic Agent	Time after Initial Bleeding	Cumulative Blood Loss	Blood Pressure	Influence on Epinephrine Reactivity	
							Plasma or serum	Liver wash (1:5)
				Hemorrhagic shock				
				min.	*% body wt.*	*mm. Hg*		
54	D156	Loose ties placed on renal pedicles (2 wks.); tied off tightly (15 min.)	Pentobarbital	28	−3.0%	51	0	
				68	−3.0	35	VDM 18 min.	
				132	−3.9	30	VDM 24 min.	
				215	0†	—	—	
				360	Death			
55	D100	R. nephrectomy (7 mo.) L.nephrectomy (70 min.)	Pentobarbital	45	−2.8%	40	0	
				190	−3.0	23	VDM 18 min.	
				220	−0.7†	—	—	
				340	Death			
56	D2	Kidneys tied off (35 min.)	Pentobarbital	45	−3.7%	60	0	
				105	−4.2	52	VDM 12 min. mild	
				165	−4.5	51	VDM 15 min. mild	
				195	−4.6	—	—	
				240	Death		VDM 30 min.	VDM 18 min.
57	D167	L. kidney* in flank (18 wks.); R. nephrec. (16 wks.); L. Kidney tied off (10 min.)	Pentobarbital	0	0.0	130	VDM 19 min. trace	
				60	−3.6%	40	VDM 24 min.	
				185	−4.7	22	VDM 36 min.	
				190	−0.5†	Death		
58	D165	L. kidney* in flank (7 wks.); R. nephrectomy (1 mo.); L. kidney tied off under procaine (20 min.)	none	40	−2.1%	67	0	
				85	−3.1	40	0	
				175	−4.4	25	0	
				200	−4.4	25	VDM 29 min.	
				240	−4.7	20	VDM 34 min.	
				255	Death		—	VDM 18 min.
59	D111	L. kidney in flank (3 wks.); R. nephrec. (10 days); L. nephrec. under procaine (16 hrs.)	none	45	−4.3%	50	0	
				165	−2.7†	30	VDM 18 min.	
				205	0†	—	—	
				310	Death		VDM 23 min. 1:1	
60	D110	L. kidney in flank (4 wks.); R. nephrectomy (8 days); L. nephrectomy under procaine (40 min.)	none	20	−2.5%	20	0	
				45	−3.2	45	0	
				105	−3.9	30	0	
				175	−4.2	30	VDM 18 min. mild	
				235	−4.8	28	VDM 24 min. mild	
				255	0†	—	—	
				405	0	97	VDM 15 min. trace	
				780	In coma‡	40	VDM 24 min. 1:1	
61	D24	L. kidney in flank (8 wks.); R. nephrec. (5 wks.); L. kidney tied off under procaine (30 min.)	none	35	−3.2%	74	0	
				65	−3.6	42	VDM 21 min.	
				125	−3.4†	53	VDM 27 min.	
				320	−3.8	20	VDM 28 min.	VDM 24 min.
				326	0†	—	—	
				600	Death			

TABLE 3.—*Continued*

Exp. No.	Dog No.	Operative Preparation	Anesthetic Agent	Time after Tour. Release	State of Animal	Blood Pressure	Influence on Epinephrine Reactivity	
							Plasma or serum	Liver wash (1:5)
Tourniquet shock								
				min.		*mm. Hg*		
62	D4	Tourniquets on 9 hrs. Renal arteries tied just before T. release	Pentobarbital	7 82 177	Coma Coma Death	65 57	VDM 14 min. mild VDM 17 min. VDM 18 min.	VDM 20 min.
63	WH17	As above except tourniquets on 8½ hrs.	Pentobarbital	30	Death		VDM 23 min.	VDM 24 min.

* Kidney covered loosely with fish skin to prevent development of collateral circulation.
† Reinfusion. Figure represents the difference between total blood withdrawn and the amount replaced.
‡ Died during night.

of the hyporeactive phase. The VDM concentrations rose progressively in the subsequent blood samples, reaching an unusually high concentration in the sample obtained at death. The saline wash of the liver removed at death not only contained VDM but produced many unfavorable side reactions in the test rat, usually indicative of cellular breakdown. The contractions which were exhibited by the small veins and venules following the injection of this sample into the test rat resembled the effects produced by the injection of potassium and are therefore designated in the chart as K^+ effects. The liver was found to have sustained a complete loss of the capacity to inactivate VDM.

2. *Tourniquet Shock following Renal Occlusion.* Two similar experiments (experiments 62 and 63, table 3) were carried out following the application of arterial tourniquets under pentobarbital anesthesia for periods of eight and one-half and nine hours respectively. The renal circulation was occluded just prior to the release of the tourniquets. As in hemorrhagic shock the hyperreactive stage was eliminated by this procedure.

A protocol is given in figure 13 of the findings in experiment 62 with dog D4 subjected to tourniquet shock after renal occlusion. The dog was anesthetized with sodium pentobarbital, 30 mg. per Kg., and arterial tourniquets were applied about both hind limbs for nine hours. Prior to the release of the tourniquets an additional 10 mg. per Kg. of pentobarbital was administered and both renal pedicles tied off. The tourniquets were released about 20 minutes after the bilateral renal occlusion. The presence of VDM in the blood sample taken seven minutes after the release of the tourniquets indicated the absence of a hyperreactive stage and the unusually rapid onset of hyporeactivity. Subsequent blood samples showed a progressive increase in VDM content. At death, the liver contained large amounts of VDM and had completely lost its inactivating capacity.

Death occurred in dog WH17, (experiment 63) with unusual rapidity, the blood pressure (which had fallen to 70 mm. prior to tourniquet release) dropped abruptly and profoundly after release of the tourniquets. The animal went into circulatory collapse within 25 minutes. The blood at this time contained VDM as did the wash of the liver removed at death.

These experiments served to establish the muscular origin of the VDM which may be present in the blood early in tourniquet shock. The rate of VDM formation in liver under complete anoxia, a phenomenon which will be dealt with in the following paper of the series, is too slow to have been responsible for the VDM content of the blood in these two animals, especially dog D4 in which VDM was present seven minutes after release of the tourniquets. Further evidence is supplied by the experiment described above (experiment 48, table 2, fig. 11) in which separate analyses were made of peripheral blood and of blood from the previously occluded limbs obtained by catheterization of the inferior vena cava.

3. *Hemorrhagic Shock following Renal Occlusion in Unanesthetized Animals.* Further

TABLE 4.—*Oxygen Consumption in Vitro of Liver and Kidney Removed from Animals in Hyper- and and Hyporeactive Stages of Hemorrhagic and Tourniquet Shock.*

Q_{O_2} = cc./Gm. wet wt./hr. Medium: Ringer Phosphate, pH 7.4

Liver				Kidney	
Exp. & Dog No.	Q_{O_2}	Exp. & Rabbit No.	Q_{O_2}	Exp. & Dog No.	Q_{O_2}
Normal dogs and rabbits					
A	0.95	a	0.81	L	2.81
B	0.92	b	0.74	M	2.66
C	0.79	c	0.67	N	2.58
D	0.76	d	0.61	O	2.52
E	0.71	e	0.58	P	2.32
F	0.71	f	0.55	Q	2.30
G	0.70	g	0.55	R	2.30
H	0.69	h	0.54	S	2.24
I	0.63	i	0.54	T	2.20
J	0.63	j	0.51	U	2.10
K	0.62	k	0.50	V	2.09
		l	0.49	W	1.91
		m	0.42		
Average...	0.74	Average.	0.58	Average.	2.34
Dogs in hyperreactive hemorrhagic shock					
6—C22	1.14			3—D114	2.46
3—D114	0.98			4—D113	2.23
4—D113	0.93			8—D157	1.93
D3	0.71 (biopsy)				
Average...	0.94			Average.	2.21
Dogs in hyporeactive hemorrhagic shock					
2A—D1	0.78			24—D158	2.30
28—D57	0.76			32—D121	2.27
D183	0.76			29—D120	2.15
D24	0.74			25—D161	2.06
58—D165	0.72				
D177	0.69				
32—D121	0.67				
16—C12	0.63				
18—C11	0.62				
23—D3	0.62				
30—C18	0.60				
31—WH7	0.59				
29—D120	0.58				
D186	0.58				
33—WH9	0.55				
C13	0.52				
17—D54	0.51				
D181	0.46				
Average...	0.63			Average.	2.20

TABLE 4.—*Continued*

Liver				Kidney	
Exp. & Dog No.	Q_{O_2}	Exp. & Rabbit No.	Q_{O_2}	Exp. & Dog No.	Q_{O_2}
Dogs and rabbits in hyporeactive tourniquet shock					
48—D35	0.81	L21	0.87	47—D32	1.80
47—D32	0.71	46—6/11	0.50	49—D12	1.74
62—D4	0.70	44—L19	0.49		
49—D12	0.64				
39—WH4	0.55				
38—WH2	0.46				
Average...	0.65	Average.	0.62	Average.	1.77

support for the participation of renal VEM in the shock syndrome was provided by resorting to renal occlusion under experimental conditions in which recovery had uniformly occurred following transfusion. Unanesthetized dogs subjected to hemorrhagic shock by graded bleeding remain hyperreactive, with VEM in the blood, throughout the syndrome and either die in circulatory collapse because of the magnitude of the blood loss or recover if transfused. The circulatory exclusion of the kidney in such animals should provide a critical test of the importance of the renal contribution to the compensatory vascular reactions of the shocked animal.

Four such experiments were carried out (experiments 58 to 61, table 3). In each the left kidney was exteriorized in the flank and the right kidney removed two to three weeks later. A period of 8 to 33 days was allowed for recovery from the second operative procedure. The exteriorized left kidney was then tied off under local procaine anesthesia prior to the induction of hemorrhage.

A representative protocol of a dog (experiment 61, table 3) prepared in this manner is given in figure 14. The total blood removed constituted 3.8 per cent of the body weight. Bioassays of blood samples drawn during the progression of the syndrome revealed the absence of VEM from the blood. A sample taken 35 minutes after the initial bleeding was neutral; within 65 minutes of the initial bleeding the blood was found to contain a high content of VDM which progressively increased with the prolongation of the hypotension. Five and a half hours after the initial bleeding, with the blood pressure at approximately 20 mm. Hg, a liver biopsy was

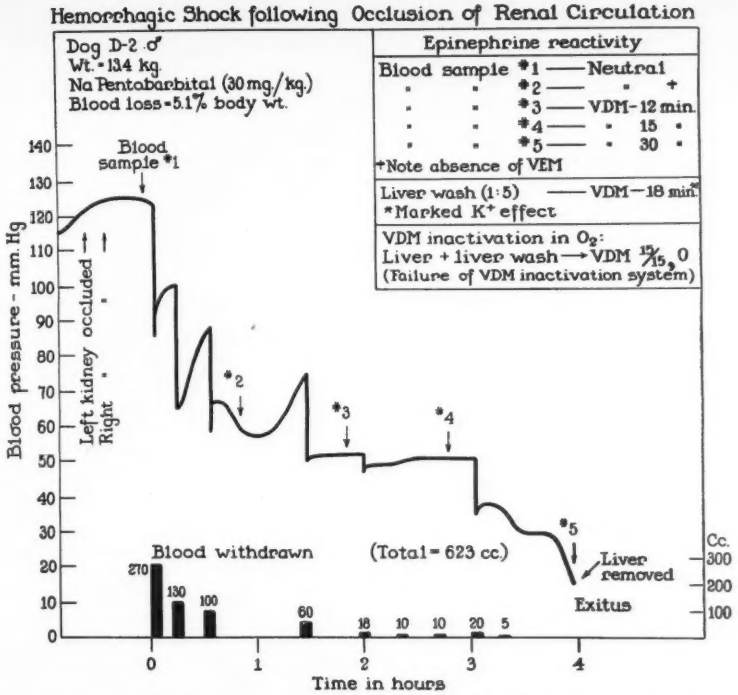

FIG. 12. Protocol of experiment 56 (table 3). Dog D2 anesthetized with sodium pentobarbital and subjected to graded hemorrhage after both kidneys had been excluded from the circulation by ties placed around the renal pedicles. Exclusion of kidneys resulted in abolition of hyperreactive phase.

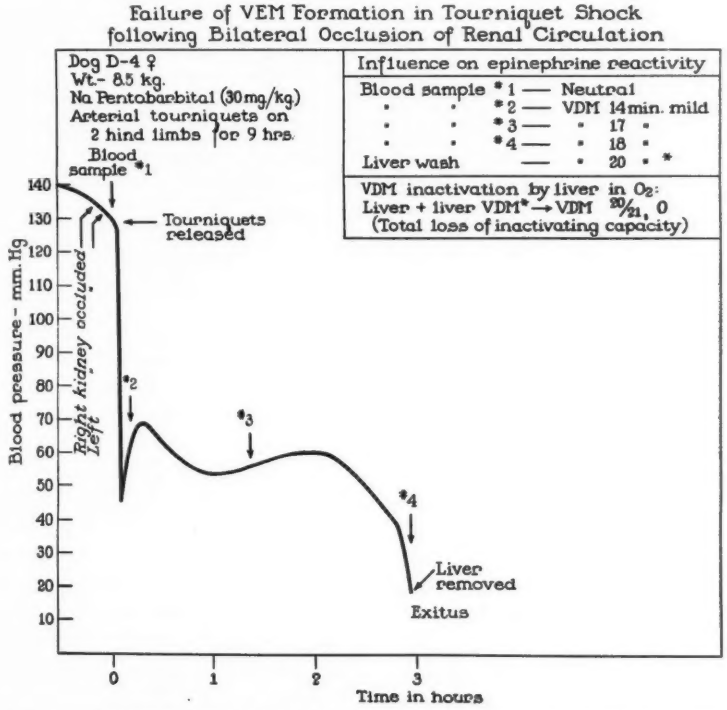

FIG. 13. Protocol of experiment 62 (table 3). Dog D4 in tourniquet shock under sodium pentobarbital anesthesia. Tourniquets were released after both kidneys had been excluded from the circulation by ties placed around renal pedicles. Note abolition of hyperreactive phase and early appearance in blood of VDM of skeletal muscle origin.

taken simultaneously with a blood sample. Both the blood and the saline wash of the liver contained large amounts of VDM. The liver was found to have sustained a profound reduction in its VDM inactivation mechanism. (The liver slices in this instance were incubated in oxygen for one hour before adding the VDM, a procedure which does not appreciably reduce the inactivating capacity of normal liver.) The animal was then reinfused with a total of 55 cc. of blood and 245 cc. of a 5 per cent serum albumin solution, equivalent to the volume of blood previously withdrawn. There followed a temporary rise in blood pressure, superseded three hours later by circulatory failure. The blood pressure chart of this animal should be compared with that of the unanesthetized dog with intact kidneys (fig. 7). In both animals the same degree of hypotension was achieved. In the unanesthetized dog with intact kidneys the blood pressure curve showed regular compensatory rises after each small bleeding, a phenomenon which is characteristic of this type of preparation. In the arenal dog, however, this phenomenon was much less marked and indeed was absent during the period of drastic hypotension.

Another phenomenon manifested by this arenal animal was the development of a state of coma from which it failed to emerge despite the replacement of the blood lost. This is in contrast with the prompt recovery of consciousness following transfusion of the unanesthetized dog with kidneys intact.[27]

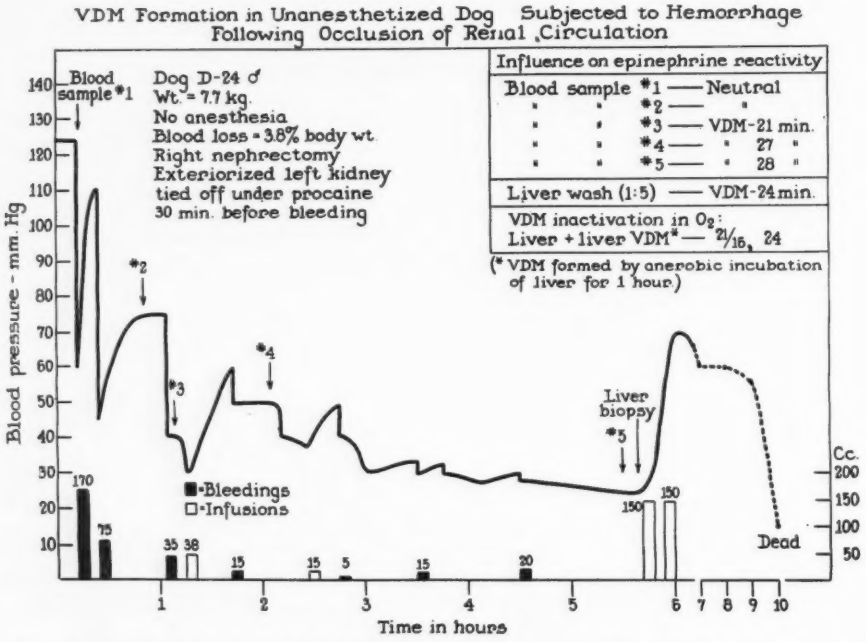

FIG. 14. Protocol of experiment 61 (table 3) dog D24, illustrates modification of hemorrhagic shock syndrome in unanesthetized dog resulting from occlusion of renal circulation. Note absence of VEM and appearance of VDM in blood one hour after initial bleeding. Liver biopsy in sixth hour showed marked impairment of VDM inactivation mechanism. Replacement therapy was ineffective in preventing circulatory failure. (Compare figure 7 for findings on unanesthetized dog with intact kidneys.)

The remaining 3 animals in this series behaved in similar fashion. Bioassays of the blood at no time showed VEM, indicating the absence of the hyperreactive stage. VDM appeared and persisted in the blood stream. There was little evidence of compensatory rises in blood pressure following bleeding throughout the syndrome. The blood withdrawn was replaced in 2 of the dogs at 205 and 255 minutes after the initial bleeding; this led to a temporary elevation of blood pressure followed by circulatory collapse. Both dogs were stuporous during the period of drastic hypotension and remained in coma despite blood replacement.

The conclusions drawn from the experiments in which the kidney was excluded from participation in the shock syndrome may be summarized as follows. In the absence of the kidney, VEM fails to appear in the blood stream at any time during the evolution of the syndrome. Under these conditions, and particularly from the experiments on hemorrhagic shock with unanesthetized dogs it would appear that the animals are deprived of the compensatory vascular hyperreactivity which prevails when VEM is present in the blood. Most conclusive is the failure of the unanesthetized animals to recover following fluid replacement therapy. More direct evidence for the dependence of compensatory vascular hyperreactivity on VEM is provided by direct visualization of the omental vessels during hemorrhagic shock in arenal animals. Such studies have been carried on in this laboratory and will be the subject of a subsequent report; they have shown that under these conditions the compensatory vascular reactivity, which occurs when VEM in present in the blood, is minimal.

Discussion

The experiments reported here have added a new metabolic derangement to the many already described as occurring in experimental hemorrhagic and traumatic shock. This disturbance involves two new sets of principles: a vasoexcitor, VEM, and a vasodepressor, VDM, whose significance stems from their relation to the compensatory and decompensatory peripheral vascular responses which occur in a regular sequence during the evolution of the shock syndrome.

The principal aims of the present study have been to clarify the tissue origins of both VEM and VDM and to establish the time relationships between their formation and the specific vascular episodes of the shock syndrome. In addition, observations are included on the state of the hepatic VDM inactivation mechanism during the evolution of the syndrome.

The sequence of humoral and tissue events relating to these vasotropic principles may be summarized as follows: The VEM activity of blood during the initial hyperreactive or compensatory phase of both hemorrhagic and tourniquet shock is of renal origin. When the syndrome progresses to the hyporeactive or decompensatory stage as a result of prolonged drastic hypotension, VEM predominance is superseded by that of the vasodepressor, VDM, whose origins have been traced to liver, skeletal muscle and spleen.

The temporal relationships have been established between the formation of these vasotropic principles and the two distinct sequential vascular episodes of the shock syndrome. The formation of VEM by kidney is initiated within 20 to 30 minutes after bleeding or tourniquet release and continues not only throughout the hyperreactive phase but also during the period of VDM predominance. However, with the prolongation of hyporeactivity the concentration of VEM in the kidney usually falls and this principle may disappear entirely. Indeed, under these extreme circumstances, the capacity of the kidney to form VEM may eventually be lost. VDM, on the other hand, can be detected in liver only after the onset of drastic hypotension which terminates the hyperreactive and ushers in the hyporeactive phase. Thereafter, until peripheral circulatory failure ensues, VDM production continues in the liver. The concentrations within the liver rise progressively and are always greater than in the blood stream. There are also parallel changes in the VDM inactivation mechanism of the liver during the evolution of the shock syndrome. This system remains intact during the initial hyperreactive phase; during the hyporeactive phase a gradual impairment to total loss consistently occurs.

Formation of these vasotropic principles by liver and kidney and the deterioration of the hepatic VDM inactivation mechanism are associated with relatively minor residual changes in the over-all in vitro oxygen consumption of these tissues. That of the kidney remains within the normal range throughout the hemorrhagic shock syndrome. Russell and associates likewise found no depression of oxygen consumption in kidneys removed from rats in hemorrhagic shock.[28] The oxygen consumption of the liver removed during the

hyperreactive phase was, on the average, in the higher range of normal; during the hyporeactive stage there was a moderate depression, averaging about 15 per cent. Similar dissociations have been described between over-all oxygen consumption in vitro and derangements in specific metabolic processes in liver such as those concerned with the inactivation of azo dyes and estrogens.[29, 30]

The extent and the time relationships of VDM formation by skeletal muscle vary with the type of procedure, whether hemorrhagic or tourniquet shock. There may be little or no formation during the hyperreactive stage of hemorrhagic shock. This may be a consequence of the usual brevity of this stage with the experimental procedure employed, since in vitro experiments have shown that VDM formation in skeletal muscle proceeds at a slower rate than in liver.[2] In addition, the VDM in skeletal muscle during the hyperreactive stage may be masked in the rat test by blood-borne VEM. Moderate amounts of VDM are usually present in muscle during the hyporeactive stage. In tourniquet shock, the extent of VDM formation in the muscles of the occluded limbs is conditioned by the period over which the tourniquets are applied, the VDM concentrations rising with time. After 8 to 10 hours of limb constriction in the dog, considerable amounts of VDM are discharged into the circulation upon release of the tourniquets. The rapidity with which this discharge occurs (as early as seven minutes) is best shown in the arenal animal in which the presence of VDM in blood is not masked by the parallel occurrence of VEM. Thereafter, and until death, the VDM content of skeletal muscle remains high. The larger skeletal muscle VDM contribution in tourniquet shock constitutes an important difference from hemorrhagic shock and may be a factor in the lower tolerance of animals in tourniquet shock to equivalent degrees of oligemia and hypotension.

The exact time of onset of VDM formation by spleen was not established. High concentrations are consistently present in spleens removed during the hyporeactive phase. It is probable that the contribution of splenic VDM to the systemic circulation in shock is negligible for two reasons: first, the markedly contracted state and reduced blood flow in the spleen throughout the shock syndrome,[23] and secondly, the action of the liver in filtering out and inactivating the VDM in the portal vein blood, thereby preventing its appearance in the systemic circulation. Furthermore, in a splenectomized, as compared with the normal dog, no difference was observed in the time of appearance of humoral VDM during the evolution of hemorrhagic shock.

In view of the multiplicity of factors involved, experiments with the living animal can provide only suggestive evidence as to the mode of origin of these vasotropic factors. In vitro studies have shown that anaerobiosis per se regularly leads to the formation of these principles by the same tissues to which their genesis has been traced in vivo. Information provided by studies on animals in shock by other workers would suggest that the tissue hypoxia which prevails during the syndrome may also be responsible for the sequential formation of these principles in vivo.

It is well established that the oligemia and hypotension of shock result in profound alterations in renal blood flow,[31, 32] the experiments of Van Slyke[33] and others being of particular relevance. In dogs under pentobarbital anesthesia, at the moderate hypotensive levels (60 to 70 mm. Hg) which we have found to be associated with the appearance of VEM in blood, they observed a prompt and marked reduction in renal blood flow. During the more drastic hypotension which leads to hyporeactivity and the replacement of VEM with VDM predominance, they found the renal blood flow, as measured by clearance methods, to be negligible. Thus renal hypoxia could account for VEM formation; and the virtual absence of a renal blood flow with drastic hypotension could contribute to the determination of the hyperreactive phase by preventing the further discharge of VEM into the general circulation. There is one additional consequence of prolonged hypotension: the reduction to complete disappearance of VEM from the kidney, and the eventual loss of the ability to form VEM,

as evidenced by subsequent anaerobic incubation of the kidney in vitro. Apparently, during prolonged anaerobiosis in vivo there is a gradual disappearance of VEM within the kidney, as well as a deterioration of the systems concerned with its formation.

It is of interest in this connection that *unanesthetized* dogs, in shock induced by the type of graded hemorrhage employed in this study, remain in the hyperreactive stage with VEM in blood throughout the syndrome, despite drastic hypotensive levels comparable to those which lead to hyporeactivity and VDM predominance in *anesthetized* dogs. This would argue for the persistence in the unanesthetized dog of some degree of renal blood flow at hypotensive levels which curtail it completely in the anesthetized dog.

Somewhat different time relationships exist for the onset of anaerobic metabolism in the liver. During periods of moderate hypotension (60 to 70 mm. Hg) in anesthetized dogs, the reduction in hepatic blood flow is apparently insufficient to initiate anaerobic processes. This is evident from the data of Van Slyke[33] and Zweifach, Hershey and associates[34] who observed no rise in blood ammonia or uric acid with this degree of hypotension. Inasmuch as both constituents are maintained at normal levels in blood by oxidative processes in the liver, the persistence of oxidative metabolism is indicated. The maintenance of aerobic metabolism in the liver in the face of a reduction in blood flow during the period of moderate hypotension may be attributable to the fact that the blood supply to the liver is ordinarily in considerable excess of its oxidative needs. This is suggested by the preservation of a relatively normal metabolism by livers in which the hepatic artery has been made the sole source of blood supply.[35] However, with the more drastic hypotension, which in our studies has been shown to be associated with VDM formation, sharp rises occur in both blood uric acid and ammonia levels. These observations are compatible with the hypoxic origin of hepatic VDM.

The same explanation could also apply to the deterioration of the hepatic VDM inactivation mechanism during the hyporeactive phase. In vitro studies have shown that a comparable deterioration follows exposure of normal liver to anaerobiosis.[2] Indeed, normal liver so treated, as well as liver removed during the hyporeactive phase, may continue to form VDM in vitro upon the restitution of aerobic conditions.[36] Wilhelmi and Long[16] have called attention to analogous defects in a variety of liver functions after profound shock in rats, as for example, the reduction in the rates of urea formation and deamination. Govier and Grieg[37] have demonstrated the destruction in the anoxic liver of several coenzymes, as well as the inactivation of the specific proteins with which these cofactors operate.

Hypoxia could likewise account for VDM formation by spleen and skeletal muscle in view of the marked reduction in blood flow through these tissues in shock.

In considering the implications of these experimental findings for the hemodynamics of shock, it is well to keep in mind the difficulty of accurately assessing the role of any one factor because of the complexity of the vascular responses to fluid loss and hypotension, and their variability under different experimental conditions. The vascular response to blood loss is of a dual character. Neurogenic factors come into play rapidly, and by virtue of their effects on the larger arteries and arterioles account for the major portion of the immediate vascular response. The local peripheral homeostatic mechanisms come into play more gradually and are potentiated by local tissue and humoral factors, such as those with which this study is concerned. The relative contribution of each of these components will, however, vary with the experimental conditions. In acute massive hemorrhage, for example, the neurogenic component may be exaggerated to such an extent that arterial vasoconstriction is almost complete and the tissues virtually deprived of blood flow. Under these circumstances there is no evidence of a significant contribution by the peripheral homeostatic mechanisms to the restriction of the peripheral blood flow. On the other hand, in shock associated with minor or very gradual blood loss, the peripheral homeostatic compensatory changes may be of major importance

from the very onset of the syndrome, with a minimal neurogenic contribution.[38] It is apparent that the subsequent decompensatory phase will also differ under the different experimental conditions cited above. Thus, circulatory failure will follow acute hemorrhage without the participation of peripheral vascular decompensatory influences, whereas the importance of decompensatory changes in local homeostatic mechanisms is emphasized by the more gradual type of bleeding utilized in the present study.

With these considerations in mind, we are now prepared to examine the extent to which our concept of shock, which is predicated on the participation of these new vasotropic factors, can provide a causal basis for the evolution of the vascular pattern which culminates in circulatory failure.

The first premise of this hypothesis is that VEM and VDM are causally related to the vascular hyper- and hyporeactivity in the mesentery. This is suggested by the passive transference to the corresponding vessels of the test rat of the same type of hyper- or hyporeactivity (as measured by the response to topical epinephrine) which is exhibited by the mesenteric vessels of the shocked dog at the time the blood sample is drawn. Somewhat more direct evidence is provided by certain of the experiments included in this study.

With respect to VEM and the compensatory adjustments to blood loss, the observations on the arenal unanesthetized dog are regarded as consonant with a causal relationship. The development in this animal, in the absence of VEM, of VDM predominance in the blood, deterioration of the hepatic VDM inactivation mechanism and irreversibility is in sharp contrast to the unanesthetized animals with intact kidneys in whom hypotension induced by the same procedures is associated with sustained VEM predominance in blood, no derangements in the hepatic VDM mechanism and persistent reversibility. In a subsequent study (to be published) involving direct visualization of the mesenteric vessels of arenal anesthetized dogs in hemorrhagic shock, it was noted that in the absence of VEM, the compensatory hyperreactivity was minimal. These findings should not be interpreted as meaning that irreversibility can not be brought about by hemorrhagic procedures in the unanesthetized dog. This condition can be induced by more drastic procedures, such as the bleeding-out and reinfusion technic of Walcott[39] and the use of the Lamson bottle procedure by Fine and coworkers[40] for the acute initiation and maintenance of drastic hypotension. We have no observations on the vasotropic content of blood during irreversible shock produced by the latter method. However, studies on unanesthetized dogs, utilizing the Walcott procedure were carried out with Nastuk and Beatty.[41] VDM occurred in almost all the animals at the point where transfusion became necessary (unpublished data). VDM disappeared from the blood of those animals which proved reversible and persisted in those which went on to circulatory collapse.

Although our observations suggest the protective character of the effects exerted by the kidney on the vascular responses to blood loss, they do not exclude the parallel contribution along with VEM of other vasoactive principles of renal origin. Angiotonin has been shown to elevate blood pressure and improve peripheral blood flow in shock.[42] The evaluation of the relative importance of these renal principles for vascular compensation must await the isolation of the factor or factors responsible for VEM acitivity and the clarification of their specific vascular effects.

Present information concerning VEM activity, based largely on the rat mesoappendix test, does not permit the inference that it is attributable to a single factor which is identical under all circumstances. Although progress has been made in the concentration of VEM activity in renal extracts by one of us (R. F. F.), no preparation has as yet been obtained with a single electrophoretic component. With respect to VDM there is direct experimental evidence that the VDM activity which appears in the blood during hyporeactive hemorrhagic shock is attributable to a single substance. The disappearance of VDM activity from such bloods following incubation with antiferritin serum provides specific immunochemical evidence for this VDM activity being ascribable to the

hepatic vasodepressor, ferritin.[24, 25] The question still remains open as to whether the VDM activity resulting from skeletal muscle hypoxia is attributable to ferritin or to another principle with similar vasotropic effects.

The second aspect, the causal relation of VDM to vascular hyporeactivity, was explored by means of experiments with tourniquet shock (9 to 10 hours) in which the tourniqueted limbs were taped or encased with plaster to minimize fluid loss. In contrast to animals with untaped limbs, the initiation and progression of the syndrome could not be attributed to a primary reduction in blood volume by extravascular leakage into the extremities which had been occluded. Direct visualization of the mesenteric vessels in previous experiments of this type[18] had demonstrated the early deterioration of the initial compensatory vascular reactions and their replacement by decompensatory behavior which progressed in typical fashion to peripheral circulatory collapse. In the experiments reported here, large amounts of VDM were discharged into the circulation by the damaged limbs from the moment of tourniquet release and thereafter throughout the syndrome. The concentrations were such as to gain predominance rapidly over the VEM which the kidneys were discharging into the blood stream. The initial abrupt fall in blood pressure may have been due in part to the opening up of the vascular bed in the occluded limbs as well as to the release of tissue breakdown products with histamine-like action and of vasodilators such as adenylic acid and adenosine compounds; but the subsequent decompensatory vascular changes could not be attributed to these specific agents. Their injection into the blood stream of the normal rat produces widespread dilatation of the larger arteries and arterioles, unlike the entirely peripheral effects of VDM.[43] Furthermore, the effects of these nonspecific vasodilators in the shocked animal are transitory and readily differentiated from the subsequent decompensatory peripheral vascular changes which persist throughout the rest of the syndrome in association with VDM predominance. The weight of evidence, despite its somewhat circumstantial character, appears favorable to the causal relation between VEM and VDM and the mesenteric vascular reactivity with which they are temporally associated, a relationship which is essential for the further development of this concept of shock.

We are now ready to examine the second major premise of this theory: that the progression of the shock syndrome to irreversibility and peripheral circulatory failure is attributable in large measure to the decompensatory vascular effects of VDM. If it could be assumed that the decompensatory vascular pattern seen in the mesentery develops to the same extent in other parts of the body, there would be no obstacle to the acceptance of this concept. However, it is highly probable that this is not the case, especially in the circulation of skeletal muscle and skin, even though the architecture of the terminal vascular bed is essentially the same as in the mesentery and the responses to VEM and VDM might be assumed to be similar. Other factors operate in the extremities, such as intense and preferential vasoconstriction and the shunting of blood directly from arteries to veins. The resultant extreme ischemia would prevent the full peripheral decompensatory pattern from developing and thereby reduce the extent to which blood is diverted into the capillary bed of these tissues. Hence this premise could only be valid (1) if the pattern of decompensatory vascular changes observed in the mesentery also developed fully in related abdominal viscera, especially the liver and gut, and (2) if the consequent local diversion of blood from the effective circulation into these organs during the latter part of the syndrome were sufficient to account for the progressive deterioration of the circulation. There is strong evidence that this is the case. During the hyporeactive stage, in contrast with the pallor and firmness of the abdominal viscera during the hyperreactive phase, the liver is engorged with poorly oxygenated blood and bleeds freely when cut; and the intestinal tract is the site of extensive congestion and hemorrhage. In the irreversible cases after transfusion this condition is usually even more marked in these organs; in addition, the kidney is often intensely congested with stagnant blood.

The importance of the alterations in the splanchnic circulation for the hemodynamics of shock has long been appreciated by workers in this field. The progressive increase in intrahepatic resistance has been securely established, as well as the reduction in the outflow of blood through the hepatic vein. This interference with hepatic blood flow would be anticipated from the ordinarily low pressure gradient through the liver. Wiggers and associates[44] point out that the blood flow through the liver in late shock is reduced to a greater extent than is suggested by changes in the systemic and portal pressures. Another consequence of the increased hepatic resistance is a profound reduction of the oxygen tension in the portal venous blood favorable to hepatic hypoxia.[16, 35] Selkurt and associates[45] have shown that an increased portal pressure per se may lead to peripheral circulatory collapse, with intestinal changes characteristic of hemorrhagic shock.

These data have been reinforced by studies involving direct visualization of the mesenteric circulation.[22] The drainage of blood by way of the large mesenteric venous channels may be used as an index of hepatoportal resistance. During periods of vascular hyperreactivity, the flow of blood in the large mesenteric veins draining into the portal system remains slowed but continuous; and following transfusion the venous drainage improves rapidly, indicating that there is no marked resistance in the hepatoportal system. In irreversible cases, as hyporeactivity develops in the mesentery, the outflow of blood through the large veins is very sluggish. Following transfusions, despite the elevation of blood pressure to levels comparable to those established in the cases which are reversible, the outflow remains unimproved or becomes even more stagnant. These observations indicate the persistence, despite transfusion, of a relatively high hepatoportal resistance during the irreversible state.

Direct visualization of the mesenteric circulation in reversible and irreversible shock has also demonstrated a consistent relationship between the vascular reactions in the mesentery and the over-all response to transfusions. Striking differences were revealed between animals which recovered and those in whom shock was irreversible. In animals with reversible shock the circulation shows an immediate improvement *before* the blood pressure has risen appreciably. Thereafter, as the blood pressure continues to rise, there is a return of the normal tone to the vessels of the terminal vascular bed and the blood distribution once more becomes confined to the preferential channels, just as in the resting state. On the other hand, in animals in which shock proves irreversible, transfusions produce a temporary improvement in blood flow only *after* the blood pressure has risen; the circulation then again begins to slow down and the blood pressure once more resumes a downward course.

The sequestration of blood within the liver and the consequent increase in intrahepatic resistance in terminal shock has had no adequate explanation for its genesis. Amongst the mechanisms suggested has been the hepatic sluice[46] by which the sphincteric contraction of the orifice of the hepatic vein might lead to pooling by increasing the resistance to venous outflow of blood from the liver. The restriction of this specific mechanism to a few species makes it inapplicable as a general explanation of this phenomenon. Intrahepatic pooling has been observed in shock in species such as the rabbit, rat and guinea pig which are devoid of such a mechanism. It is here suggested that this pooling may be ascribed to high concentrations of VDM within the liver, acting locally to bring about decompensatory vascular changes similar to those observed in the mesenteric vessels. As has been pointed out above, increased intrahepatic resistance and pooling do not occur during the hyperreactive phase but only in association with mesenteric vascular hyporeactivity and VDM formation within the liver. This is in direct accord with the logical development of our concept. Knisely has called attention to the large number of sphincters in the vascular bed of the liver.[47] These occur at the proximal and distal ends of the sinusoids traversing the liver lobules. They are also particularly abundant at the arteriovenous anastomoses of the terminal divisions of the portal vein and hepatic artery

just before they drain into the sinusoids. These sphincteric arrangements permit wide fluctuations in the relative amounts of arterial and portal venous blood passing through the liver lobule. In addition, these sphincters by their relaxation would expand the capacity of the vascular bed and provide the mechanism for extensive pooling within this highly vascular and expansible organ. The temporal relationships between pooling and VDM formation within the liver would suggest that VDM may be the specific local stimulus for sphincteric relaxation.

Skeletal muscle trauma, caused in these experiments by tourniquet occlusion, results in the early release of muscle VDM into the circulation and introduces a variable which modifies the time relationships of intrahepatic pooling. This stems from the ability of the liver to filter out VDM from the blood stream and to accumulate high concentrations locally prior to the onset of liver hypoxia and hepatic VDM formation. The selective accumulation of VDM from the blood stream by the liver (unpublished data) is evidenced by the high concentrations of VDM in the liver of eviscerated rabbits at a time when there is none remaining in the blood stream following the intravenous injection of a VDM concentrate. A similar accumulation was also noted in the taped limb experiment previously described. Such an accumulation of VDM in the liver and its local circulatory consequences should predispose the liver to the hypoxia which in turn initiates local VDM formation within that organ.

Once this entire set of decompensatory vascular changes has fully developed in the splanchnic area, the animal has become irreversible to transfusions. In our concept of shock, the ineffectiveness of transfusions at this stage is postulated to be a consequence of their failure to reverse the metabolic derangements of the VDM and VEM mechanisms, and their resultant decompensatory vascular effects. The observed persistence or even exacerbation of these specific metabolic and vascular defects is compatible with this postulate. Following transfusion there will usually be a temporary reduction or even an abolition of VDM activity in the blood, presumably due to the effects of dilution and to other properties of blood now under investigation. This is accompanied by a temporary improvement in the mesenteric circulation. Thereafter the concentration of VDM in the blood rises and remains elevated, with a return of the full decompensatory pattern in the mesentery, until collapse ensues.

Relevant studies in the literature indicate that it is unlikely that transfusions can effectively increase the blood flow through the liver at this stage. Observation on the mesentery following transfusions show no improvement in the flow in the large mesenteric veins despite the elevation of blood pressure to nearly normal levels and a rapid inflow of blood on the arterial side. The failure to correct the intrahepatic hemodynamic state would result in the persistence of local hypoxia and VDM formation and provide an explanation for the recurrence of VDM in blood after transfusion. However, even though the blood flow could be restored to the liver during this stage, as by the viviperfusion procedures of Frank, Seligman and Fine,[40] the restoration of oxidative conditions per se within the liver need not be effective in correcting the derangements in VDM metabolism. In vitro experiments have shown that once damage to the VDM inactivation mechanism has been sustained it is not repaired by the restoration of oxidative conditions for periods up to three hours; and the liver continues to form VDM in oxygen. Hence this defect of the VDM inactivation system may become critical for the ultimate recovery of the circulation. These inferences are reinforced by the failure of Fine and co-workers[48] to reverse the syndrome at this stage by direct arterial perfusions of the liver through the splenic vein for as long as two hours.

These observations are also relevant to the findings in the type of viviperfusion experiment in which the blood from the shocked animal is passed through the circulation (including the splanchnic area) of a normal dog before being returned to the donor animal, without influencing the downward course of the shock syndrome. The question has been

raised as to why the liver of the normal recipient should not have corrected the VDM disturbance in the shocked animal.[48] It is apparent from the above data that merely clearing the blood of VDM does not rectify the metabolic defect in the liver of the shocked dog.

Evidence of another type suggesting the relation of VDM to the development of peripheral circulatory collapse is furnished by previous studies with rabbits which were partially eviscerated, leaving intact the hepatic arterial supply to the liver.[49] Several rabbits which had developed profound hypotension for about 60 minutes following accidental blood loss during evisceration, were restored by blood transfusions until normotensive levels were sustained. They were then injected with a hepatic VDM concentrate prepared by Dr. A. Mazur of this laboratory. In contrast with the rapid disappearance of VDM from the blood of uncomplicated eviscerated preparations, high titers of VDM persisted and there was a progressive fall in blood pressure to shock levels. In these rabbits the initial period of shock and the associated hypoxia of the liver prior to transfusion, had apparently damaged the VDM inactivation system sufficiently to prevent the liver from inactivating this principle. More direct evidence of the specific relation of VDM to peripheral vascular decompensatory behavior would be desirable. The recent identification of hepatic and splenic VDM with ferritin will permit experiments of a more direct and specific character.

All the above evidence pointing to the critical significance of the liver for the development of irreversibility is in agreement with the viviperfusion experiments of Frank, Seligman and Fine.[40, 48] These investigators carried out the viviperfusion experiment in two ways, delivering arterial blood from the normal donor dog into a recipient dog either directly to the liver via the splenic vein, or to the general circulation via the jugular vein. The transfusions were started soon after bleeding by a standard procedure, with a view to maintaining aerobic conditions in the liver in the first group of animals. Equivalent degrees of hypotension led to recovery in the former, whereas the animals transfused via the jugular died.

The kidney may also undergo changes during the development of irreversible shock which are not corrected by transfusion and which may contribute to the eventual circulatory collapse. Loss of the capacity to form VEM deprives the animal of a factor which could assist in the restoration of a normal peripheral circulation. It is also noteworthy that the kidney, in common with the other abdominal viscera, may become congested following unsuccessful transfusion. The dilatation and pooling within this organ probably results either from the absence of vasoconstrictor influences of local or neurogenic character or from the presence of a positive deleterious vasodepressor factor, such as VDM. However, the relation of VEM and VDM to these unfavorable intrarenal vascular phenomena must, for the present, remain speculative.

Recent experiments by Reinhard, Glasser and Page[50] are interpreted by them as evidence against the liver or kidney playing a significant role in the shock syndrome. Dogs were hepatectomized, with or without the prior removal of the kidneys, subjected to a period of hemorrhagic hypotension and then retransfused. The criteria utilized were the restoration of blood pressure to control levels, the return of the pressor response to intravenous epinephrine, and the shed blood volumes. The complicated character of the experiments did not permit the use of other conventional criteria, such as recovery of the animals, the experiments being of relatively short duration, with a post-transfusion period of one and one-half to four and one-quarter hours. It is doubtful whether the data provided by these experiments can be used to resolve the problem of the role of hepatorenal factors in shock. This is implicit in the authors' statement that they "believe it desirable to avoid the terms 'shock' or 'irreversible shock' as they apply to hepatectomized animals while they do not in any case long survive." Glasser and Page[51] utilizing the same procedure for the induction of hemorrhagic shock in normal dogs reported survival percentages varying unpredictably from 23 to 76 per cent. These

authors state that the nature of the factors responsible for these differences in survival is uncertain. The inadequacy of their criteria was more evident in the case of animals with favorable prognosis. A second objection to the hepatectomy experiments stems from the probable effects of the prolonged preliminary surgical procedures on the kidney. These animals are actually subjected to shock upon two separate occasions, once in the course of the hepatectomy with its attendant trauma and extensive hemorrhage and again following the experimental bleeding procedure. The initial operative shock would discharge renal vasotropic factors and restrict renal blood flow. This prior depletion of the kidney undoubtedly limits the further renal contribution to the vascular responses during the subsequent hemorrhagic procedure. Hence it is doubtful whether any real difference would be introduced by surgical nephrectomy. These reservations would also apply to the experiments of Bobb and Green[52] from which it was concluded that the kidney exerted no protective role in traumatic shock. Even more questionable is the relation of the hemodynamics of a hepatectomized animal to the responses of the normal animal in hemorrhagic shock. This reservation applies also to the experiments in which blood from shocked animals was introduced into hepatectomized or hepatectomized-nephrectomized animals after a period of hemorrhagic hypotension. Our previous discussion has called attention to the wealth of evidence which has accumulated to establish the critical contribution of the hepatoportal and mesenteric circulatory phenomena in shock. Our own findings reinforce this conclusion and are contrary to the interpretations which Reinhard, Glasser and Page give to their experiments.

Conclusions

1. Studies have been carried out in dogs and rabbits subjected to hemorrhagic and tourniquet shock for the purpose of determining the tissue origins of two newly described vasotropic principles, VEM and VDM.

2. The vasoexcitor principle, VEM, which predominates in blood during the hyperreactive or compensatory phase of shock was traced to the kidney. The vasodepressor principle, VDM, which prevails during the hyporeactive or decompensatory phase, was found to originate in liver, skeletal muscle and spleen.

3. Time relationships have been established for the formation of these vasotropic principles in their tissues of origin. VEM is formed by kidney with considerable rapidity after shock induced either by hemorrhage or by the application of tourniquets. Its formation continues throughout the syndrome, though it may diminish in magnitude and cease if the period of drastic hypotension is greatly prolonged. VDM formation by liver is initiated by the drastic hypotension which terminates the hyperreactive phase, and continues throughout the hyporeactive phase until circulatory collapse ensues. During the hyporeactive phase there is a parallel deterioration of the hepatic mechanism for inactivating VDM.

4. Formation of VDM by spleen also occurs during the hyporeactive phase.

5. Skeletal muscle VDM is formed slowly during the progression of hemorrhagic shock but participates to a considerable degree in tourniquet shock as a consequence of its prior formation during the application of the tourniquets. It is suggested that the lessened tolerance to oligemia and hypotension of animals in traumatic as compared with hemorrhagic shock may be due to the greater contribution of skeletal muscle VDM to the former syndrome.

6. The sequential tissue hypoxia during shock may be responsible for the formation of these vasotropic principles, as well as for the deterioration of the hepatic VDM inactivation system. This is consonant with in vitro observations that anoxia per se leads to the formation of these principles by the same organs.

7. A concept of the hemodynamics of experimental shock has been advanced, based on the participation of these vasotropic principles. Experimental evidence has been obtained to support the concept that VEM may be causally related to the initial hyperreactivity, and VDM to the subsequent decompensatory hyporeactivity associated with irreversibility to transfusion.

8. The significance of VDM predominance

and the deterioration of the VDM inactivation mechanism have been stressed. Special emphasis was placed on the probable effects of local concentrations of VDM within the liver, and on the resultant diversion of blood from the general circulation as a consequence of its sequestration in the splanchnic viscera.

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Studies on the Effect of Oral and Parenteral Administration of Visammin (Khellin) in Patients with Angina Pectoris

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Of 20 carefully studied patients with angina pectoris given oral visammin, 4 had a significant reduction in number of pains. Eleven stated that their pains were less severe and less easily precipitated while taking visammin. There was questionable improvement in the exercise tolerance test in 2 of 9 patients after oral visammin therapy. The daily oral dose ranged from 40 mg. to 240 mg. Undesirable side effects were encountered in 17 of the 20 patients. Parenteral administration of visammin was evaluated by means of the ballistocardiograph, the exercise tolerance test, and by tilting.

Introduction

KHELLIN, now officially called visammin,[1] has been reported to be a potent coronary vasodilator in animal experiments.[2, 3] Anrep, Kenawy, and Barsoum[4] have summarized the history, pharmacology, and early clinical trials with the drug. In addition they found distinct clinical improvement in 140 of 250 patients with angina pectoris that were treated with visammin. Ayad[5] reported good results with visammin in 19 of 23 patients treated. Rosenman and co-workers in a series of 14 patients with angina reported a good response to visammin in eleven.[6] Osher and Katz[7] reported subjective or objective improvement in 16 of 19 patients. Greiner and Gold,[8] however, in a comparative study on patients with angina have found visammin to be no better than placebo.

In order to evaluate further the therapeutic value of visammin in angina pectoris, the present study, employing both subjective and objective means on a group of controlled patients, was undertaken.

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Methods and Materials

Twenty-three patients who presented a reliable and typical clinical story of angina pectoris were selected from the Cardiac and Medical Clinics of the Cincinnati General Hospital for studies with oral and parenteral administration of visammin. Each patient was given a small card made in the form of a calendar on which he was instructed to enter the number of pains during each day. All patients were allowed to take nitroglycerin tablets as often as they needed. Some patients required maintenance digitalis and this medication was not changed. These patients were observed by one of us for a control period up to six weeks prior to the administration of either visammin or placebo.

The effect of oral administration of visammin (40 mg. per tablet) and of a placebo of identical appearance was compared in 20 patients. The preparations were dispensed by the same physician who did not know the nature of the tablet. After a first period of trial which averaged five weeks (range of two to eleven weeks) with either visammin or placebo, the medication was changed. In some patients a third and a fourth period of trial with either visammin or placebo were carried out.

Exercise tolerance tests were carried out on all patients except those few with a history of recent myocardial infarction. The test was performed as follows: the patient walked over two steps with an ice cube in each hand up to the point of angina or severe dyspnea.[9, 10, 11] An electrocardiogram* including standard leads, unipolar extremity leads, and precordial leads V_4 or V_5 was taken prior to and immediately after completion of the exercise. In most instances at least two exercise tolerance tests

* Sanborn Visocardiette

were performed on different days during the control period. The exercise test was repeated after the completion of the trials with visammin and placebo.

Parenteral administration of visammin (50 mg. per c.c.) was evaluated by means of the following objective technics: the ballistocardiograph, the exercise tolerance test, and tilting.

Cardiac output was determined in 8 patients, usually within three hours after a light meal, by means of a high frequency ballistocardiograph[12] before and after the intramuscular injection of visammin. The cardiac output was determined in 2 additional patients before and after a comparable injection of saline. All patients rested for at least 15 minutes before injection. The dosage of visammin used varied from 100 to 400 mg. Records were obtained at five minute intervals for 30 to 60 minutes. Heart rate was determined from the electrocardiographic record and blood pressure was measured by the auscultatory method.

The exercise tolerance test was performed on 5 patients after the intramuscular injection of 150 to 200 mg. of visammin.

The effect of parenteral visammin on the pressor and depressor blood pressure reflexes induced by tilting was investigated in 6 patients, using the technic developed in this laboratory.[13] The intra-arterial blood pressure response was determined before and for periods up to 45 minutes following the intramuscular injection of 200 mg. of visammin.

Results

Clinical Effect of Oral Administration

Four of the 20 patients experienced fewer anginal attacks while receiving oral visammin (table 1, cases 1, 2, 3, and 4). One of these (case 3) had fewer attacks of angina during a five week period of visammin. During a subsequent period of visammin therapy and without apparent increase in activity, this patient experienced more severe angina and developed a myocardial infarction.

Sixteen patients showed no significant difference in average number of pains per week while on visammin or placebo therapy (table 1, cases 5–20).

Whereas improvement in the actual number of pains was not impressive, 11 patients (table 1, cases 1–11) stated that while taking visammin their pains were either less severe or less easily precipitated. Seven patients (table 1, cases 12–18) were enthusiastic about both visammin and placebo; 2 even chose placebo in preference to visammin as giving them more relief. Two patients (table 1, cases 19–20) felt that visammin did not help.

Exercise Tolerance Tests

Exercise tolerance tests were performed sixty-one times on 19 patients.* A positive test as indicated by the appearance of angina was obtained in 9 of these patients during the control periods. A positive test as indicated by RS-T segment depression of 0.5 mm. or more in any lead, a change in direction of the T waves, or conduction defects[14] was obtained on one or more occasions in all 19 patients during the control period; 6 of these patients were on digitalis at the time of the test, making the interpretation doubtful.[15–17]

Exercise tolerance tests were performed on 9 patients following oral administration of visammin, and on 5 patients following parenteral administration of visammin; in 6 of these patients exercise tolerance tests were performed after administration of placebo. There was improvement in the exercise test in only 2 patients during the course of oral visammin therapy.

Case 4 (C. W.) made twenty trips on one trial and nine trips on a second trial during the control period; after five weeks of oral treatment with 120 mg. of visammin per day, he performed thirty-one trips. There were positive electrocardiographic changes after each test. Case 12 (R. H.) performed eight trips and sixteen trips on two tests during the control period; after seven and one-half weeks of oral administration of visammin averaging 40 mg. per day, he performed twenty-six trips; nevertheless, the RS-T segment depression in the electrocardiogram was not lessened after therapy. None of the patients showed increased exercise tolerance or diminished electrocardiographic changes following placebo medication. One patient, Case 8 (S. S.), showed less marked RS-T segment depression in the standard and precordial leads following 175 mg. of visammin intramuscularly than he had shown on previous tests; the onset of pain was not delayed.

* Tabulation of the results of the exercise tolerance tests has been omitted becuase of space limitations. The table will, however, be available with the authors' reprints.

TABLE 1.—*Results of Oral Studies with Placebo and Visammin*

Patient	Age Sex Race	Diagnosis	Duration of Angina	Periods of Study							Remarks
				Control		Placebo		Visammin			
				Weeks	Average Attacks per Week	Weeks	Average Attacks per Week	Weeks	Average Attacks per Week	Average Dose per Day	
										mg.	
1. W. S.	54 M W	ASHD Myocardial infarct	2 yrs.	1½	29.4						
								7	9.7	96	Enthusiastic about visammin. Able to spade garden without pain.
						5	21.0				
								4	6.0	160	
2. M. M.	45 F N	Hypertension	1½ yrs.	5	23.8						
								5	31.2	84	Very enthusiastic about visammin.
						6	16.8				
								4	16.7	92	
								3	7·7	120	
				2	13.5						
3. W. P.	54 M W	ASHD Myocardial infarct	12 yrs.	2	85.6						
								2	71.5	120	Enthusiastic about visammin at first. Later experienced infarct and died.
								4	27.6	86	
						½	Almost constant				
								1½	91.7	168	
4. C. W.	39 M N	Hypertension	5 yrs.	1	25.0						
						2	23.0				Prefers visammin to placebo. Pains less frequent and less severe.
								5	24.0	120	
								3	25.0	160	
								3	16.0	240	
5. J. M.	77 M W	ASHD	11 yrs.	2	27.0						
						8	18.8				Thinks visammin has helped him "somewhat."
								6½	15.3	120	
								4	17·0	160	
								2	14.0	240	
6. D. M.	65 M W	ASHD Hypertension Old myocardial infarct	7 yrs.	8½	1.1						
								5	0.6	56	Prefers visammin to placebo. Able to walk farther without pain.
						3	0.7				
				5	0.8						
7. M. R.	72 F W	ASHD Hypertension; Diabetes	9 yrs.	2½	9.6						
								7½	6.7	17	Prefers visammin to placebo.
				13	3.7						
						4	2.5				
8. S. S.	62 M W	ASHD Hypertension. Old posterior infarct	6 yrs.	4	5.5						
								10½	3.0	44	Prefers visammin to placebo. Able to walk farther without pain.
						6	2.5				
								1	3.0	40	
				8	2·2						
9. G. S.	65 M N	Hypertension	4 yrs.	6	1.0						
						5	1.2				Prefers visammin to placebo.
								5	0.6	120	
								4	1.2	120	
				5	0						

TABLE 1.—*Continued*

Patient	Age Sex Race	Diagnosis	Duration of Angina	Periods of Study							Remarks
				Control		Placebo		Visammin			
				Weeks	Average Attacks per Week	Weeks	Average Attacks per Week	Weeks	Average Attacks per Week	Average Dose per Day	
										mg.	
10. D. H.	52 F N	Hypertension	1 yr.	5	24.4	7 4	31.6 32.3	6 1 3	23.7 35.0 26.0	112 160 240	Prefers visammin to placebo. Pains less frequent and less severe.
11. M. P.	67 F W	Hypertension and recent myocardial infarct	9 yrs.	4	35.0	3 1	0 0	7½ 1 4	1.5 0 0	40 40 40	Very enthusiastic about enteric visammin. Can walk farther without pain.
12. R. H.	56 M N	Hypertension. Old cerebrovascular accident	4 yrs.	6 2	1.5 5.0	9	0.2	7½ 2	0 0	40 120	Enthusiastic about both.
13. M. Wil.	51 F N	Hypertension ASHD	8 yrs.	2	5.0	11	2.2	5 4	2. 0.5	1 84 115	Both visammin and placebo helped. Prefers visammin.
14. N. G.	63 M W	ASHD	8 yrs.	4	0.5	7	0.7	14	0.3	40	Both visammin and placebo helped. No preference.
15. A. H.	72 M W	Hypertension	2 yrs.	2	3.5	9	1.2	11½ 5	3.2 1.0	52 120	Very enthusiastic about both visammin and placebo.
16. W. Sch.	71 M W	Hypertension. Auricular fibrillation	8 yrs.	2 4	6.5 0.5	2½ 4	0 0	6	2.8	60	Both visammin and placebo helped.
17. C. N.	69 M N	ASHD	1½ yrs.	2 4½	6.0 2.6	6	0	5½	4.5	120	Very enthusiastic about both. Prefers placebo.
18. M. Wav.	60 M N	Hypertension. Incomplete RBBB	6 mos.	5	1.7	8½ 5	1.3 0.4	5 4	1.2 0	120 120	Both helped. Prefers placebo.
19. E. W.	66 M W	ASHD	4 yrs.	3½ 4	5.0 1.1	1	2.0	3	2.9	30	Neither visammin nor placebo helped.

TABLE 1.—*Continued*

Patient	Age Sex Race	Diagnosis	Duration of Angina	Periods of Study							Remarks
				Control		Placebo		Visammine			
				Weeks	Average Attacks per Week	Weeks	Average Attacks per Week	Weeks	Average Attacks per Week	Average Dose per Day	
										mg.	
20. W. Sa.	62 M W	ASHD Latent Syphilis	1 yr.	4	5.8	—	—	2	7.0	120	Visammin did not help.
21. M. O.	49 F N	Hypertension	4 yrs.	2	18.5	2	20	—	—	—	While on placebo experienced a subendocardial infarct.
22. H. P.	51 M W	ASHD Aortic stenosis. Old infarct	5 yrs.	3½	8.6	2	Pains worse	—	—	—	Pains worse on placebo. Would not return.
23. P. D.	58 M N	Hypertension. Old infarct	9 yrs.	3½	3.2	2	0	—	—	—	Pains helped by placebo. Has not returned.

ASHD = Arteriosclerotic heart disease (coronary sclerosis).
The sequence of periods of study are illustrated by the horizontal subdivisions.

Ballistocardiography

Four of the 8 patients who received visammin had abnormal control ballistocardiographic records. Cardiac output was not computed in these four.[18] However, no change in contour or amplitude of the ballistocardiographic complexes occurred after the injection of visammin.

The remaining 4 patients had normal records permitting calculation of cardiac output. One showed an increase over 10 per cent of the basal value, while 3 demonstrated a decrease after parenteral visammin. These changes in cardiac output were transient. The interval between time of injection and the occurrence of maximal change in cardiac output varied.

In the 2 control subjects, in whom saline placebos were substituted for visammin, no significant change in cardiac output was observed.

No significant change in the blood pressure or pulse rate was noted following intramuscular administration of visammin. All patients receiving visammin intramuscularly complained of burning pain at the site of injection.

Tilting

The reflex blood pressure responses to tilting were studied in 6 patients (cases 5, 6, 8, 9, 15, and 23). The pattern of response was identical before and after the intramuscular injection of 200 mg. of visammin. It is interesting that all of these patients had an increased or a normal depressor response, since other studies[19] have shown the depressor response to be absent or decreased in more than 50 per cent of patients with hypertensive and arteriosclerotic heart disease.

Reactions

Seventeen of the 20 patients treated with oral visammin experienced one or more undesirable reactions. Nausea, anorexia, epigastric burning, dizziness, and diuresis were encountered most frequently (table 2). One patient (R. H.), while on a dosage of 120 mg. daily for seven days developed a rather severe reaction consisting of marked nausea, weakness, and profuse diuresis with the loss of five pounds.

There seemed to be an individual variation

in susceptibility to the quantity of visammin producing side reactions. These reactions were encountered in 5 patients who were taking as little as 40 mg. per day and were so annoying that 3 stopped taking the drug. Thirteen of 17 patients who were given 120 mg. per day experienced side reactions. There were 3 patients in the series, however, who were able to take 240 mg. per day with no untoward effects.

A few patients have noted the onset of side reactions after taking as few as three or four 40 mg. tablets. More frequently, however, a greater number of tablets usually were taken before untoward effects began to be noticed.

Enteric-coated visammin was administered to 7 patients. There was no difference in the incidence of side effects from this form as compared with regular visammin except in 1 case. This patient (case 11, M. P.) experienced anorexia and epigastric burning on a daily dose of 40 mg. of regular visammin but could take the same dose of enteric-coated visammin without difficulty.

A somewhat surprising finding was that 9 patients developed side reactions while on placebo medication. These reactions consisted of nausea, epigastric burning, and gaseous distention. The sugar coating of the tablet could not be implicated as a cause.

Discussion

It is well established that the evaluation of any therapeutic agent in angina pectoris is extremely difficult because of the variable course of the disease process. Such factors as excitement, fatigue, environmental temperature, meals, and the development of collateral circulation [20–26] affect the number and frequency of anginal seizures and cannot be satisfactorily controlled. In addition the relationship between the physician and the patient may influence the response to a drug.

We have attempted to overcome some of these difficulties. Each patient was observed for a control period prior to the administration of any preparation. The duration of study was for periods up to 11 months in some patients, thus helping to minimize the influence of seasonal temperature variation. The same physician followed the patients and administered all medication. This physician did not know whether he was administering visammin or placebo until the study was completed. Many of the patients had been instructed in the past to take nitroglycerin tablets in anticipation of pains. Therefore, the number of actual attacks of angina pectoris was used as a criterion of frequency of seizures rather than the number of nitroglycerin tablets used. In addition an attempt was made to compare the severity of attacks in a given patient before and after visammin therapy.

Table 2.—*Side Reactions Encountered with Visammin*

Reaction	No. of Patients	Dosage Range of Visammin
		mg.
Nausea	14	40–160
Dizziness	7	40–120
Diuresis	6	40–120
Anorexia	4	40–240
Epigastric Burning	4	40–120
Pyrosis	2	40–120
Abdominal Cramps	2	80–120
Gaseous Distention	2	40–120
Diarrhea	1	120
Constipation	1	240
Weakness	1	120
"Smothering"	1	120
Numbness in Arms and Legs	1	120
"Sick all over"	1	120
Insomnia	1	120
Drowsiness	1	40

Improvement due to visammin therapy has been determined in a number of ways by various investigators. Anrep, Kenawy, and Barsoum[4] described a marked reduction in frequency of attacks in 140, a moderate reduction in 85, and no change in 25 of 250 patients studied. Rosenman, Fishman, Kaplan, Levin, and Katz,[6] using both a decrease in the number of attacks and a decrease in the number of glyceryl trinitrate tablets taken as an index of improvement, found good results in 11 of 14 patients. Osher and Katz,[7] using the number of nitroglycerin tablets taken per week as a guide to the frequency of attacks, found improvement in 16 of 19 patients. Our results differ markedly from those obtained by the above investigators in that a decrease in the

number of attacks was observed in only 4 of 20 patients while on visammin therapy.

Rosenman and co-workers[6] also state that there was increased capacity for exercise and increased sense of well-being while on oral visammin in 11 of 14 patients studied. Subjective improvement of this nature occurred in 11 of our 20 patients.

The exercise tolerance test has been employed as an objective means of measuring response to visammin therapy. Unfortunately, there has been no universally accepted method of performing the test, which makes comparison of results difficult. Anrep and co-workers[4] performed the test by having the patient step on a chair at a uniform rate until pain appeared. In all patients tested, they found an increased performance with the prevention of RS-T depression and T-wave inversion after intramuscular injection of 100 mg. of visammin. Dewar and Grimson[27] carried out the test by having the patient walk up and down a standard flight of stairs until anginal pain was produced. They found that visammin in oral doses of 150 mg. (120 mg. by improved assay)* prevented or diminished anginal pain in 10 of 12 patients studied and prevented or resulted in decreased electrocardiographic changes in 7 of 9 cases. Osher and Katz,[7] using the two step test as described by Riseman and Stern[9] found increased performance after courses of oral visammin in 16 of 19 patients.

Employing the modified two step test as already described, we found only 2 patients of 11 tested who showed even questionable improvement in performance after oral visammin. One of the 5 patients given intramuscular visammin showed less marked RS-T segment depression after exercise than he had shown following control tests.

Whereas we have not found the consistently high percentage of subjective and objective improvement noted by these investigators, it is our opinion that there were patients in our series who were definitely improved by visammin. Our findings are in this respect more encouraging than the negative results reported by Greiner and Gold.[8] There may be several possible explanations for these discrepancies. The course of angina, as has already been mentioned, is variable and extremely difficult to study. The methods of evaluation of response employed by the various workers have all been slightly different. However, the most apparent reason for the discrepancies in the reports lies in the dosage employed.

Osher and Katz employed 120 mg. or more per day in all cases who showed improvement. Rosenman and associates used as high as 300 mg. (240 mg. by improved assay) per day in 9 of their 14 patients. We were not able to administer such high doses in as large number of patients because of the high incidence of side reactions in our series. None of the side effects we encountered were considered severe except in one patient (case 12, R. H.). Nevertheless, they were sufficiently troublesome that many patients were unable to take the prescribed number of tablets every day. It may be that because of this, a sufficiently high therapeutic drug level was not adequately maintained in all cases. As can be seen in table 1, 2 patients (cases 7 and 19) were able to take on the average of less than one tablet (40 mg.) per day. Four patients were able to take one tablet per day. In all likelihood, therefore, none of these was maintaining an adequate therapeutic level. All of these patients fell in the category of showing no improvement in the number of pains experienced. One patient (case 2, M. M.) who, when taking on the average of 84 mg. per day, showed no improvement, but had rather pronounced improvement on 120 mg. per day. Patient C. W. (table 1, case 4) did not show any reduction in the frequency of his pains until he was given 240 mg. per day. Greiner and Gold[8] administered 100 to 150 mg. (actually 80 to 120 mg.) per day in their studies.

The therapy with this drug must be largely individualized to the patient. Some patients seem to get subjective improvement on an average daily dose of between two and three tablets, while others require larger doses. It is suggested that the daily dose be started at 40 mg. three times per day, after meals. If at the end of two weeks there is no improvement, the dosage should be increased, providing the occurrence of side effects is not too distressing,

* Personal communication from Smith, Kline, and French Laboratories.

to first 160 mg. and, if necessary, to 240 mg. per day. The administration of aluminum hydroxide preparations has helped reduce the incidence of gastric disturbances in some cases.

It would appear that this drug may have definite therapeutic possibilities in angina pectoris, but that at present there are limitations because of the occurrence of unpleasant side reactions in some patients which prevent their taking an adequate dose. From our studies, it is suggested that an average daily dosage of one or two tablets (40 or 80 mg.) is inadequate. It is hoped that forms of visammin now being developed will have fewer side effects and thus permit the administration of higher dosage levels.

Summary and Conclusions

1. The effect of oral administration of visammin was studied in 20 patients with angina pectoris. The method of investigation included a control period of observation and alternate periods of placebo and visammin therapy. The total period of observation averaged six months for each patient.

2. Only 4 of the 20 patients had a significant reduction in the number of anginal attacks while receiving oral visammin; however, 11 stated that their pains were less severe and that they were able to do more work.

3. There was questionable improvement in performance as measured by the exercise tolerance test in 2 of 9 patients studied after oral visammin.

4. Cardiac output as measured by the ballistocardiograph following intramuscular visammin increased in only one of 8 patients.

5. Pressor and depressor blood pressure reflexes induced by tilting showed no change after parenteral visammin in 6 cases studied.

6. Undesirable side effects were frequently encountered and were more common with daily dosages of 120 mg. or more.

7. We believe that visammin does have therapeutic value in the treatment of angina but that at present the high frequency of undesirable side effects prevents many patients from taking an adequate dose to achieve benefit.

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A Comparison of Coronary Flow Determined by the Nitrous Oxide Method and by a Direct Method Using the Rotameter

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Coronary flow per minute per 100 Gm. of heart with venous drainage into the coronary sinus as measured by the nitrous oxide procedure was compared in the dog with left coronary artery inflow per 100 Gm. of heart perfused by this artery as measured by the rotameter. The error arising from epicardial leak of nitrous oxide was prevented or quantitated by appropriate coverage of the heart. Extremes of the comparisons were +21 and −22 per cent, with an average variation of ±12.4 per cent. The nitrous oxide method is regarded as giving semiquantitative coronary flow values per 100 Gm. of left heart in the dog.

THE NITROUS oxide procedure for determination of cerebral blood flow in man[1] has been employed for measuring coronary blood flow in the anesthetized and unanesthetized dog[2, 3] and man.[4] In this method, catheters are placed in an artery and in the coronary sinus (the major venous drainage channel of the left heart), and flow per minute per 100 Gm. of heart with venous drainage into the coronary sinus is determined by a variation of the Fick principle. The denominator of the Fick equation is found by computing the integrated difference between the concentrations of nitrous oxide in arterial and in coronary sinus blood during a period of equilibration with a 15 per cent concentration of nitrous oxide. The numerator is assumed to be equal to the product of the venous concentration of the gas (after equilibrium is established) and the partition coefficient of the gas between myocardium and blood. The accuracy of this method for quantitating coronary flow has been tested in the anesthetized dog with the bubble flow meter as the reference method.[2] Although satisfactory agreement is reported in such comparisons, coronary inflow was intermittently measured through only a branch of the left coronary artery (which constituted only a portion of the blood draining into the coronary sinus); a time lag of approximately one minute existed between the arterial blood passing through the bubble flow meter and that flowing through the uncannulated branch of the left coronary artery; and the venous samples for the nitrous oxide method were withdrawn from a cannula tied into the great cardiac vein, which prevented possible contamination of coronary sinus blood by blood from the right atrium. Because of the importance of this procedure as the only available method permitting measurement of coronary flow in the unanesthetized state, the necessity for confirmation of its accuracy is apparent.

The present investigation is an evaluation of the nitrous oxide method for measuring coronary blood flow by comparison with measurement of total left coronary artery inflow by a rotameter[5] when the venous blood samples for the nitrous oxide procedure were withdrawn from a catheter lying free in the coronary sinus. The rotameter was used as the standard of reference, since it measures blood flow directly, continuously, and with a high degree of accuracy.

METHODS

Flow measurements were made simultaneously by the nitrous oxide and the rotameter methods in 15 to 25 Kg. dogs, anesthetized with sodium pentobarbital, 20 to 30 mg./Kg., intravenously. Using artificial positive pressure respiration, the chest was opened by removal of portions of the third to seventh left ribs. The pericardium was incised over the origin of the left coronary artery, the artery carefully cleaned at its origin, and a suture passed around it. In earlier experiments coagulation was prevented by an in-

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jection of pontamine fast pink (150 mg./Kg.) and heparin (10 mg./Kg.); in later experiments by heparin alone (10 mg./Kg.). In each experiment half the initial injection was repeated every 30 minutes.

Simultaneously to measurement of coronary flow by the nitrous oxide procedure, total left coronary inflow was determined directly by metering flow through the left coronary ostium with an optically recording rotameter (fig. 1). Blood was led from a trocar in a carotid artery through the rotameter, and then into the left coronary artery by a cannula inserted into it via the brachiocephalic artery and aorta, and tied in place.[6] Except during the period of the actual test, blood was shunted around the rotameter. Time for blood to pass through the rotameter circuit approximated six seconds. Immediately after the test run, and in some experiments also dyes (0.5 per cent Evans blue and 1.4 per cent picric acid) simultaneously and at equal pressures of 100 to 150 mm. Hg into the right and left coronary arteries. Thus, left coronary flow per 100 Gm. of dyed heart was determined and could be compared with the flow value obtained with the nitrous oxide procedure.

For the venous samples in the nitrous oxide procedure, a catheter with tip varying from No. 4 F to 6½ F was inserted 3 to 5 cm. into the coronary sinus via the external jugular vein, either with fluoroscopy before opening the chest, or visually and by palpation after exposure of the heart. For the arterial samples a catheter of identical capacity was attached to the efferent tube of the rotameter near the coronary cannula. The incised pericardium was not closed and the heart was thus partially exposed to the atmosphere. Just before the comparative test, the

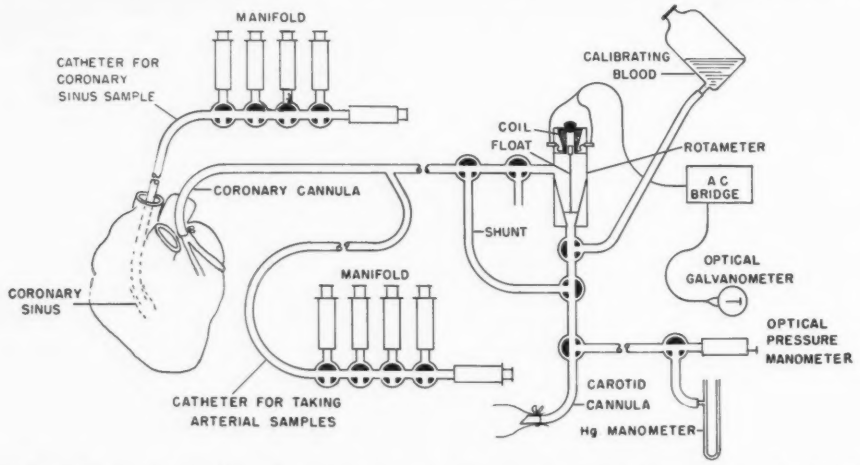

FIG. 1. Schematic drawing of arrangement of apparatus for measuring coronary flow by the nitrous oxide and rotameter methods.

before, the rotameter was calibrated with the dog's own blood at essentially body temperature and at the viscosity prevailing during the run. Mean flow per minute was calculated by planimetric integration of the area under the recorded flow curve, a correction being applied for the volume of blood drawn from the efferent tube of the rotameter for arterial samples and clearing of the catheter. Heart tissue fed by the left coronary artery was determined by weighing the amount of tissue (moist weight) taking up blue stain following injection of 0.5 per cent Evans blue dye through the left coronary artery cannula. This injection was made (1) by introducing the dye at a low pressure into the blood flowing into the coronary artery ante mortem, and then immediately inducing ventricular fibrillation; (2) by similar dye injection post mortem; (3) by removing the heart with the left coronary artery cannula still in place, cannulating the right coronary artery, and injecting contrasting dog was connected to a tank of nitrous oxide mixture which activated a second artificial respirator previously adjusted to approximately the same rate and depth as the compressed air respirator. During administration of the nitrous oxide mixture (15 per cent nitrous oxide, 64 per cent nitrogen, 21 per cent oxygen), blood samples were drawn manually into oiled syringes containing enough heparin solution to fill the terminal dead space. Periods of measurement of coronary flow ranged from 10 to 15 minutes. Samples were withdrawn throughout the first minute, and then for half-minute periods at 1.5, 3, 5, and 10 minutes, respectively, and in some experiments also at 7, 12, and 15 minutes. Immediately after withdrawal the syringes were capped, placed in ice water, and within two to four hours the nitrous oxide content of each sample was determined in duplicate, using the method of Orcutt and Waters[7] as modified by Kety.[8] Flow comparisons were ex-

pressed as per cent deviation of the nitrous oxide flow values from the rotameter flow values.

After a group of experiments had been performed using the above technic, it was found that nitrous oxide could escape from the exposed surface of the heart. Therefore the following method was used to quantitate this escape. Dogs (12–20 Kg.) were anesthetized and the chest opened as before. The heart was covered by an appropriate material impervious to nitrous oxide, consisting of a latex rubber sac or a glass cardiometer, or the pericardium was avascularized and left intact.* The pericardial space was then filled with saline or air, the nitrous oxide mixture was administered for 10 to 15 minutes, and the concentration of nitrous oxide in the pericardial space at the end of this period was compared with that before administration of the gas. It was arbitrarily assumed that the volume of gas escaping from the left heart was equal to the product of total nitrous oxide collected and the ratio of left heart weight to total heart weight. Coronary flow was determined simultaneously by the nitrous oxide method during saturation as described above except that arterial samples were withdrawn from a catheter passed into the aorta.

A final group of experiments was then performed in which this leak of nitrous oxide was prevented or quantitated (and a correction applied to nitrous oxide flow values). These nitrous oxide flow values were compared with left coronary inflow as measured by the rotameter. Technic was identical with that of the first group of experiments except that after the animal had been prepared for an experiment, but before the nitrous oxide mixture was administered, the incised pericardium was carefully sutured and either the incision was made impervious to gas with collodion, or a latex sac was fitted about the entire pericardium and evacuated. In 3 dogs 10 to 20 cc. of fluid was found in the pericardial space at the end of the nitrous oxide run. This was measured, analyzed for nitrous oxide, and a correction applied to the nitrous oxide flow value. After the run had been completed, in 4 dogs the pericardium was widely reopened to expose the heart, and after a 30 minute period for complete elimination of nitrous oxide, the experiment was repeated

Results

In the initial 15 comparisons of flow in 10 dogs, the pericardium was left open and the heart was partially exposed. In the individual experiments the mean flow measured by the rotameter was either constant or showed a mild decrease during the test period. Under different dynamic states the rotameter flow per 100 Gm. dyed heart varied from 36 to 130 cc. per minute. The comparisons varied at random from extremes of +50 per cent to − 18 per cent, with an average variation between the two methods of ±17 per cent (data not shown). These comparisons may not be valid, since after their completion it was found that nitrous oxide could diffuse through the epicardium in significant amounts.

In the second series of experiments the amount of nitrous oxide leaking from the left heart surface was calculated and compared with the amount of nitrous oxide absorbed by the left heart at equilibrium. Typical results are shown in table 1. Approximately 0.1 to 3.0 cc. of nitrous oxide leaked through the myocardial wall of the whole heart, irrespective of whether the atrial appendages were within or without the sac (20 experiments). When the left ventricular surface alone was covered, about 0.7 cc. of nitrous oxide was recovered from the surface of the left ventricle (3 experiments). Simultaneous measurements showed that this estimated leak of nitrous oxide from the left heart varied from 2 to 100 per cent of the nitrous oxide calculated to have entered the left heart during the determination of coronary flow with the nitrous oxide method. The concentration of nitrous oxide around the heart was indirectly related to the volume of the surrounding fluid or gas, and its concentration progressively rose during the 10 minute saturation period to reach a maximum of 1.0 to 4.0 volumes per cent. This maximum concentration was always considerably less than that in the coronary artery or in the coronary sinus.

In the final group of experiments comparative tests were made of the rotameter and nitrous oxide methods, first when this potential error was eliminated or controlled by an epicardial barrier, and then with the left ventricle partially exposed. Coronary flow values as measured with the rotameter were essentially constant or decreased slightly during the experiments. The data in four comparative tests (table 2) show that partial exposure of the

* The natural or rubber pericardium was shown to be essentially nonpermeable to nitrous oxide by failure to recover the gas from a glass cardiometer filled with saline, whose opening was closed with one of the membranes and which was immersed for 10 to 15 minutes in saline with a nitrous oxide concentration of 5 to 10 volumes per cent.

left heart causes the coronary flow as measured by the nitrous oxide method to be relatively lowered. This is in the direction of change which would be expected if the nitrous oxide leak comes from the left coronary vascular bed. Presumably, this epicardial leak arises from the cardiac exposure which was used in testing the nitrous oxide method. The probability that it occurs in the normal animal or human is somewhat remote.

With this potential error under control, nine comparisons (table 2) between the two flow methods vary between extremes of +21 per cent and −22 per cent, with an average variation of ±12.4 per cent.

Discussion

Under the conditions of these experiments, a considerable difference exists between the coronary flow per minute per 100 Gm. of heart with blood supply draining into the coronary sinus (nitrous oxide method) and coronary flow per minute per 100 Gm. of heart fed by the left coronary artery (rotameter method). The scatter of results must be explained on the basis of errors in the two procedures and/or in their comparison.

In the nitrous oxide procedure, the technical error in determining the nitrous oxide arteriovenous difference can be judged from the fact that the average difference of duplicate nitrous

Table 1.—*Measurement of Nitrous Oxide Escaping from the Surface of the Heart.*

Date	Pericardium	Volume Saline (S) or Air (A) cc.	N_2O Escaped cc./10 min.	N_2O Calc. Abs. by Left Heart cc./10 min.	N_2O Coronary Flow cc./100 Gm./min.	Est. Error Per cent
1/17/50	Natural	10 S	0.29	5.9	140.0	4.0
1/30/50	Natural	10 S	0.22	4.4	59.4	4.0
2/2/50	Rubber	10 S	0.13	7.4	69.9	1.4
2/3/50	Rubber	10 S	0.35	7.4	69.8	3.8
2/27/50	Rubber (L.V.)*	35 S	0.66	7.5	80.4	9.0
2/28/50	Rubber (L.V.)*	76 S	0.76	3.2	42.5	24.0
1/26/50	Glass	100 S	2.12	3.9	67.6	43.0
1/27/50	Glass	80 S	1.10	5.8	62.9	15.0
1/30/50	Glass	58 S	1.25	3.8	59.4	26.0
2/16/50	Glass	110 A	1.94	6.5	47.9	24.0
2/17/50	Glass	63 A	2.88	4.9	65.4	47.0

* Left Ventricle.

Table 2.—*Comparison of Nitrous Oxide and Rotameter Flow Values.*

Date	Mean B.P. mm. Hg	Heart Weight (Gm.)		Left Coronary Blood Flow cc./min./100 Gm.			Comments
		Total	$\frac{\text{Left*}}{\text{Total}}$ %	N_2O	Rotameter	$\frac{N_2O\text{-Rot}}{\text{Rot}} \times 100$	
3/ 2/50	110	159.0	79	72.0	85.0	−15	Pericardium. 20 cc. fluid.
3/ 3/50	100	105.3	85	83.6	107.0	−22	Pericardium. 10 cc. fluid.
	102			57.4	76.6	−25	Exposed.
3/ 8/50	82	105.9	79	59.3	56.3	+5	Pericardium + latex sac. No fluid.
3/ 9/50	130	104.5	84	90.8	75.0	+21	Pericardium + latex sac. No fluid.
	124			77.4	80.0	−3	Exposed.
3/21/50	92	138.7	84	88.2	79.0	+11	Pericardium + latex sac. No fluid.
	101			68.0	64.2	−6	Exposed.
4/10/50	83	162.1	81	44.0	41.4	+6	Pericardium + latex sac. 14 cc. fluid.
	81			41.6	43.5	−4	Exposed.
5/ 2/50	52	149.2	82	42.5	36.4	+17	Pericardium + latex sac. No fluid.
5/ 5/50	111	152.9	79	75.0	85.2	−12	Pericardium. No fluid.
5/ 8/50	91	121.5	83	62.6	64.5	−3	Pericardium + latex sac. No fluid.

* Left heart injected by dye which always included entire left atrium, left ventricle, interventricular septum and the peripheral fringe of the right ventricle.

oxide analyses for the 120 pairs was 0.030 volumes per cent, the maximum difference being 0.065 volumes per cent. Such differences can possibly introduce an error approximating ±5 per cent, since the mean nitrous oxide arteriovenous difference during a test run varied in different experiments from 0.55 to 1.3 volumes per cent, with an average difference of 0.8 volumes per cent. Errors could also arise from entrance into the coronary sinus of blood from the nonmuscular tissue of the heart, from the right atrium, or from the left ventricular cavity via thebesian and arterioluminal vessels; from diffusion of nitrous oxide through the endocardial wall into the left ventricular cavity; or from participation of nitrous oxide in the metabolic processes of the heart. Whether any of these errors actually exist would be difficult to determine and quantitate.

With the use of the rotameter the technical error is small. The rotameter used in these experiments has been shown to measure flow within ±3 per cent in the presence of considerable variation in flow pattern, blood viscosity, and blood temperature. The rotameter value per 100 Gm. of dyed heart can also be in error from over- or under-injection of the myocardium. The magnitude of this error is difficult to determine. However, it is believed that the dyed heart weight is an accurate index of weight of cardiac muscle supplied with flowing blood by the rotameter, since in 23 injected hearts the percentage of total heart weight dyed by the injection varied between the narrow limits of 78 to 85 per cent, irrespective of whether injection was made through the left coronary artery during life or post mortem, or simultaneously into both right and left coronary arteries (see table 2).

The calculated rotameter flow value can differ from the nitrous oxide flow value because the two methods do not measure flow through the same myocardial area. The rotameter flow value is based on the weight of the injected heart tissue (i.e., that supplied by the left coronary artery) which approximates 78 to 85 per cent of the total heart weight and is essentially all left heart (90 to 95 per cent), including all the left atrium, left ventricle, septum, and the peripheral fringe of the right ventricle. The nitrous oxide flow value is based on the nitrous oxide content of the coronary sinus blood and is a measure of the flow per minute through 100 Gm. of heart whose blood flow drains into the coronary sinus. This blood in the coronary sinus constitutes only 70 to 80 per cent of left coronary inflow and does not include the 20 to 30 per cent of left coronary inflow draining by the anterior cardiac veins of the right ventricle into the right atrium.[9] In addition, in the dog occasionally up to 12 per cent of coronary sinus blood can come from the right coronary artery.[6] However, this drainage is presumably not significant in our experiments, since comparison between the two methods was favorable when right coronary artery drainage into the coronary sinus was encouraged by reducing left coronary inflow 30 to 40 per cent with a screw clamp on the rotameter tubing during approximately half the period of the run (table 2, experiments 5/5/50 and 5/8/50).

Despite the multiplicity of possible errors in the nitrous oxide procedure, the method is believed to indicate semiquantitatively coronary flow per minute per 100 Gm. of left heart.

Although this work was performed on operated animals, there is no reason to believe that the degree of accuracy which has been demonstrated for the nitrous oxide method will be altered in the unanesthetized dog.

Summary

Coronary flow per minute per 100 Gm. of heart with venous drainage into the coronary sinus as measured by the nitrous oxide procedure was compared in the dog with left coronary artery inflow per minute per 100 Gm. of heart perfused by the artery as obtained with the rotameter. The error arising from epicardial leak of nitrous oxide was prevented or quantitated by appropriate coverage of the heart. A considerable difference was still found to exist between comparative values under different hemodynamic states, the extremes of comparisons being +21 and −22 per cent, with an average variation of ±12.4 per cent. The nitrous oxide method is regarded as giving semiquantitative coronary flow values per 100 Gm. of left heart in the dog.

ACKNOWLEDGMENTS

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Cavity Potentials of the Human Ventricles

By HENRY A. ZIMMERMAN, M.D., AND HERMAN K. HELLERSTEIN, M.D.

Intracavitary potentials of the human left ventricle were studied in 8 patients by the technic of retrograde ulnar artery or, in one case, pulmonary vein catheterization. The intracavitary potentials from the left ventricle were of the QS variety and confirm Wilson's concept of the earlier depolarization of the intraventricular septum from left to right.

IN RECENT years the genesis of the human electrocardiogram has been clarified as a result of catheterization of the right side of the heart.[1] The fundamental concepts of Wilson and others, based upon dog experiments, have been amply substantiated in practically all respects. However, in man, proof of the earlier depolarization of the left side of the upper part of the interventricular septum has been based upon the demonstration of an R wave in the right ventricular cavity, and upon the assumption that an R wave would be absent in the corresponding region of the left ventricular cavity. The answer to this problem is now afforded by electrocardiograms obtained from the cavity of the human left ventricle by the technic of left heart catheterization.[2] The first left ventricle catheterization was done on October 8, 1948.

METHODS

The intracavitary potentials of the left ventricle of 9 male patients were obtained, 8 by the technic of retrograde ulnar arterial catheterization,[2] and one by passing a catheter electrode through a pulmonary vein into the cavity of the left ventricle at the time of operation for pneumonectomy. In 5 of 8 patients, the right ventricle was also catheterized in the usual fashion[3] at the same time and intracavitary electrocardiograms recorded. The Sanborn Viso-Cardiette and Stetho-Cardiette were used to record the electrocardiograms.

To avoid damaging the aortic valve leaflets, patients with functional and organic insufficiency of the aortic valve were selected for retrograde ulnar arterial catheterization. Earlier attempts to bypass the normal aortic valve were uniformly unsuccessful.[4] In 6 patients, the aortic insufficiency was of syphilitic origin, and in 2 hypertensive patients there was functional aortic valvular insufficiency presumably due to dilatation of the aortic ring. There was an average pulse pressure of 98 mm. Hg, and the usual auscultatory and dynamic signs of aortic insufficiency were present. The patients ranged in age from 48 to 74 years. Only 2 were on digitalis therapy. Safety precautions included ample sedation and continuous observation of the cardiac mechanism by means of a direct writing electrocardiograph during the procedure. The patients withstood the procedure well and suffered no immediate or delayed ill-effects from the arterial catheterization.

In most patients, the electrocardiographic data were supplemented by determination of intracavitary pressures by means of Statham strain gages. A No. 6 Cournand single lumen catheter was advanced to the desired position. A continuous stream of heparinized saline was forced through the catheter at approximately 180 mm. Hg pressure. Intracardiac tracings were obtained with the column of blood or saline acting as a linear conductor.[5] In several patients, a single lumen catheter with an indwelling spring steel stylet 3 to 5 mm. from the end of the catheter was used. The potential variations recorded in this fashion were definitely those taking place at the tip of the catheter, and resembled tracings obtained from the arm end of the catheter lumen when the stylet was removed. In the latter instance, there was some distortion due to stray 60 cycle current and the amplitude of the deflections was about one-half as great as when the stylet was close to the distal orifice of the catheter.

In 6 of 8 patients, the catheter entered the left ventricle with ease; however, in 2 patients, the tip was obstructed by the deformed aortic valve leaflets. Tracings obtained in the proximal part of the arch of the aorta, just above the valve leaflets, resembled those taken with the tip of the catheter in the cavity of the left ventricle.

The position of the tip of the catheter was determined in several ways: (a) by fluoroscopy, (b) from the form of the pressure curve, and (c) by the marked increase of voltage when the catheter tip entered the cavity of the ventricle. Numerous records were obtained in various parts of both ventricles; particular interest was focused on the region of the upper interventricular septum. A technic originally employed by one of us (HKH) in dog experiments was successfully employed in this study.[6] As

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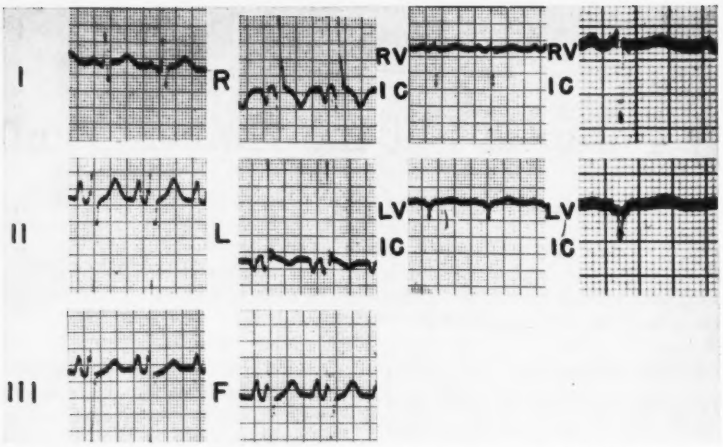

FIG. 1. Three limb leads, three augmented leads and the cavity potentials from the right and left ventricles of a white male with syphilitic aortic insufficiency without evidence of congestive heart failure. The left precordial leads (not shown here) exhibited negative ST-T complexes. Note that the cavity leads are negative and the right arm and left arm leads have net positive values which indicates that the right arm "unipolar" lead does not measurably reflect true cavity potentials in this case. The magnified curves in the last column show more clearly the detail of the complexes.

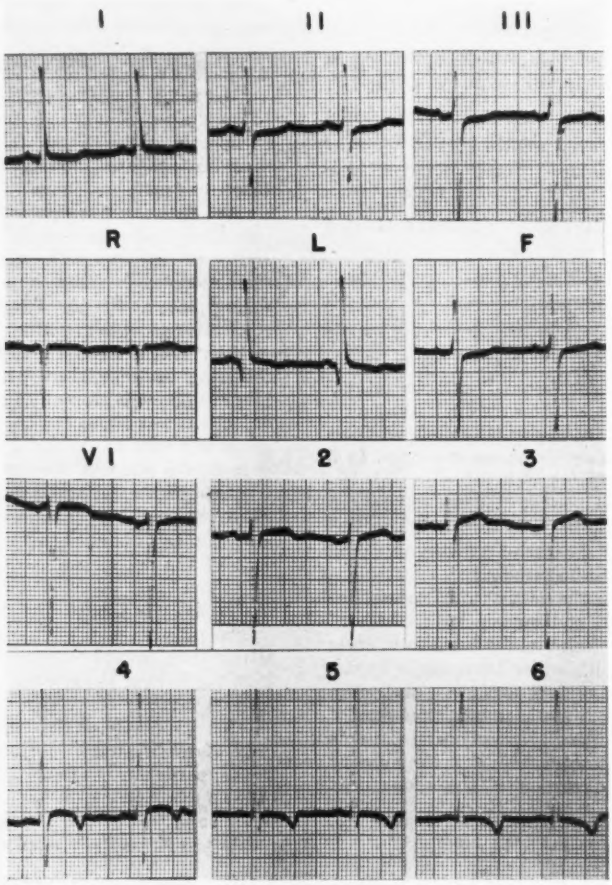

FIG. 2. Routine twelve lead electrocardiogram taken precatheterization from C. S., a Negro male with syphilitic aortic insufficiency in congestive failure at the time of study.

the catheter was withdrawn from the tip of the left ventricle to the left arm, and from the pulmonary artery to the right arm, continuous electrocardiographic tracings were recorded. In this way changes in form and amplitude of the electrocardiogram were noted and correlated with the position of the tip of the catheter as ascertained by continuous fluoroscopic observation. In several patients, roentgenograms of the chest were obtained with catheters in place in both ventricles. In addition to intracavitary electrocardiograms, standard, "unipolar" limb, and precordial leads were obtained.

The 8 patients studied by arterial catheterization had marked left ventricular hypertrophy, and the other patient, studied during pneumonectomy, had both right and left ventricular hypertrophy. In one patient intraventricular conduction was prolonged (0.12 second), on the basis of left ventricular hypertrophy, and in all others, the duration of the QRS complexes was 0.11 second or less.

Results

Intraventricular Electrocardiograms. In the right ventricle in the region of the upper part of the interventricular septum, the intracavitary electrocardiogram showed a small positive deflection followed by a large negative wave, i.e., an rS complex. Tracings of the rS variety were obtained when the catheter tip entered the right ventricle from the right atrium and when the catheter tip was withdrawn from the pulmonary artery into the outflow tract of the right ventricle. This initial positivity has been observed by others and has been attributed to the earlier activation of the upper portion of the interventricular septum from left to right.[1, 7, 8] In the corresponding region of the left ventricle, the intracavitary tracing was in each instance of the QS variety, with an initial slurring on the downward limb, apparently corresponding to the R wave of the right ventricular lead (figs. 1, 4, 6 and 11). In no case was a positive deflection recorded within the left ventricle in this region. These observations confirm Wilson's concept of the earlier activation of the uppermost part of the left side of the septum.

However, in one case, a positive deflection was recorded in the tip of the apex of the cavity of the left ventricle (fig. 4, no. 1, 5). The complex was of the rS variety, and the positive deflection was most conspicuous when there was S-T elevation due to endocardial pressure injury. When the catheter was withdrawn about 1 cm., a small negative deflection appeared, which preceded the R wave, and the ventricular complex was of the QRS variety. Several minutes later, the complex reverted to the rS form, with persistence of the positive deflection, although injury effects had disappeared. The positive deflection in this isolated instance may have been due to (1) depolarization of the lower septum from right to left, (2) manifestation of injury current of depolarization, or (3) orientation of the tip of the catheter electrode so that it would be "facing" the wave of depolarization passing down the Purkinje system. The possibility of the latter was suggested by earlier dog experiments. Hellerstein and Liebow[9] have noted that when an intracavitary electrode was pressed gently against the endocardium of the left ventricle, a positive deflection occurred, without manifestations of injury in the S-T segment. When pressure was released, this small positive deflection disap-

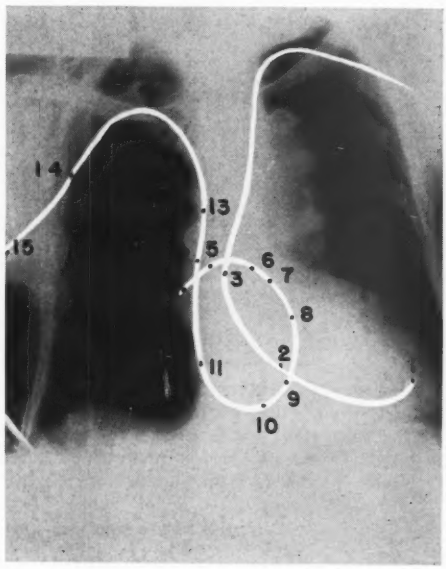

Fig. 3. Roentgenogram of patient, C. S., showing indwelling cardiac catheters with their tips in the right pulmonary artery and in the apex of the left ventricle. The numbers refer to positions of the tip of the catheters at which records in the following figures were obtained.

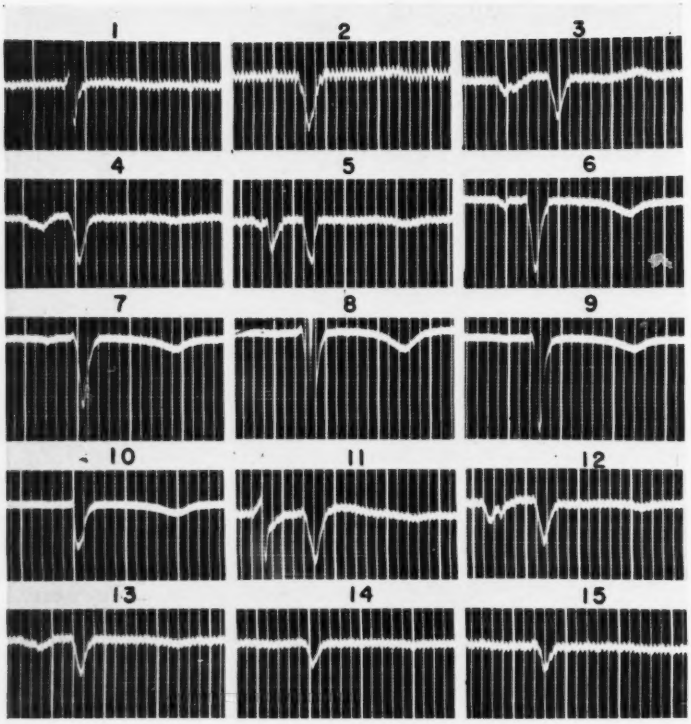

FIG. 4. Fifteen curves taken at the levels shown in figure 3.

Curve 1 is from the apex of the left ventricle at N/15 sensitivity recorded from position 1, figure 3. The complex is unusual being of the rS variety and is discussed in the text.

Curve 2 was taken from the upper left ventricle just below the aortic valve ring at N/15 sensitivity from position 2, figure 3. Note the absence of the r wave and slurring of the downward limb of the QS complex.

Curve 3 was taken from the ascending aorta just above the aortic valve at N/15 sensitivity from position 3, figure 3. Note the broad negative P wave, QS complex, and positive T wave. The record resembles the tracing within the left ventricle, and not that of the right ventricle. The right arm unipolar lead differs from the left cavity and aortic leads in that the T wave is oppositely directed.

Curve 4 was taken from the right pulmonary artery at N/3 sensitivity from position 4 in figure 3.

Curve 5 was taken from the right pulmonary artery at N/3 sensitivity from position 5 in figure 3. The position fluoroscopically corresponded to the same level as curves 3 and 12. Note the similarity of the complexes.

Curve 6 was taken from the main pulmonary artery, near the bifurcation at N/3 sensitivity from position 6, figure 3. Note the increase in amplitude of the complexes.

Curve 7 was taken from the pulmonary artery just above the pulmonic valve at N/3 sensitivity from position 7, figure 3. A positive deflection now is more conspicious (rS complex) and is found in all tracings in the right ventricle. Presumably tracings from positions 4 and 5 resemble left cavity potentials closer than those from the right arm and right atrium.

Curve 8 was taken from the outflow tract of the right ventricle below the pulmonary valve at N/3 sensitivity from position 8, figure 3. Note the increase in amplitude of the complexes.

Curve 9 was taken from the mid right ventricle at N/6 sensitivity from position 9, figure 3.

Curve 10 was taken from the right ventricle below the tricuspid valve at N/3 sensitivity from position 10, figure 3.

Curve 11 was taken from the mid right atrium at N/3 sensitivity from position 11, figure 3.

Curve 12 was taken from the lower superior vena cava at sensitivity N/3, from position 12, figure 3.

Curve 13 was taken from the mid superior vena cava at N/3 sensitivity from position 13, figure 3.

Curve 14 was taken from the right axillary vein at N/3 sensitivity from position 14, figure 3.

Curve 15 was taken from the brachial vein at the level of the mid-upper arm at N/3 sensitivity from position 15, figure 3.

peared. Presumably in these experiments, the altered spatial orientation of the exploring electrode to the oncoming excitation wave spreading down the Purkinje system was responsible for the positive deflection.

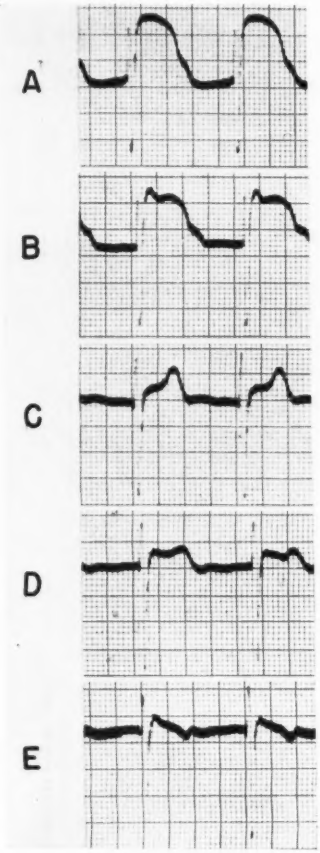

FIG. 5. An injury current produced by pressure of the tip of the catheter against the endocardium of the apex of the left ventricle. Curves A, B, C, D, and E are portions of a continuous record taken as the catheter was withdrawn one centimeter. Note the return of the S-T segment toward the isoelectric line. The origin of the R wave is obscure and is discussed in the text.

Endocardial Pressure Injury Effects. Typical monophasic curves of injury were recorded when the tip of the catheter came in contact with the endocardium of either the right ventricle or the left ventricle (fig. 5). The muscle region affected was minute, since distant leads were uninfluenced. Upon withdrawal of the catheter for 1 to 2 cm., the injury effect subsided promptly, similar to the findings in animals.[6]

Electrocardiograms from the Root of the Aorta. Tracings obtained in the aorta above the aortic ring and from the ascending portion of the arch of the aorta reflected the left intraventricular potentials. The complexes were of the

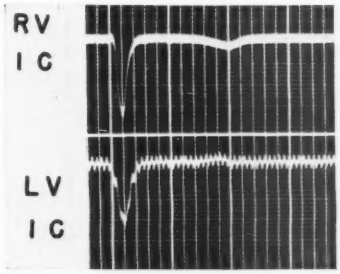

FIG. 6. Curves from the right and left ventricular cavities. The curves were synchronized by the use of heart sound tracings recorded simultaneously.

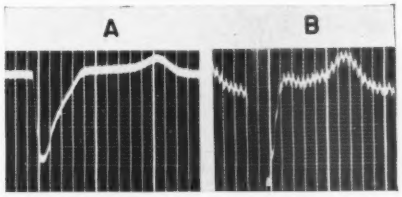

FIG. 7. The similarity of premature ventricular beats when recorded locally. Curve A is a right ventricle premature beat recorded by a right intraventricular lead. Curve B is a left ventricular premature beat recorded by a left intraventricular lead. Note the similarity of the QS complexes and the positive ST-T areas.

QS type in the arch, and in the root of the aorta of the QS or Qr form (fig. 8). The delayed positive deflection probably reflected the later activation of different portions of the base of the left ventricle. The direction of the ST-T complex (S-T segment displacement, or T wave) was opposite in sign to that found in the lateral precordial leads; elevated in aortic and left intraventricular leads, and depressed in leads V_4, V_5 and V_6. The potentials within the left ventricle were greater than those from

within either the right ventricle, the aorta, or from the anterior chest wall as registered by of the catheter in the ventricle has been noted above.

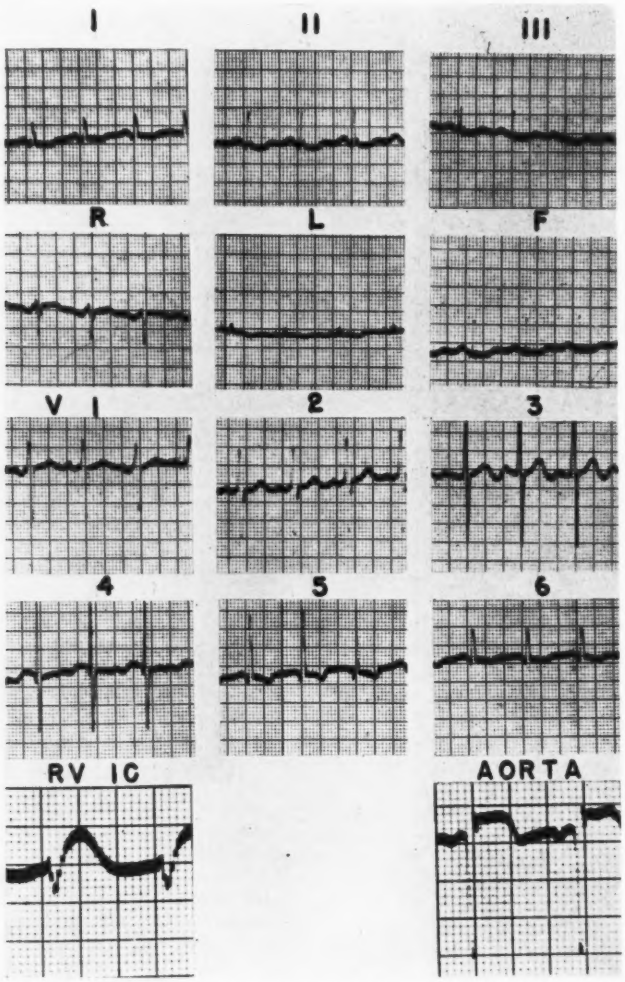

FIG. 8. Tracing taken from J. L., a white male with malignant hypertension, and functional aortic valvular insufficiency. The patient was not in congestive cardiac failure nor had he been taking digitalis. Shown here are the conventional twelve leads, a lead from the right ventricular cavity and a lead from the lower portion of the ascending aorta. The aortic valve in this patient could not be bypassed. Tracings obtained from the ascending aorta shows S-T elevation and Qr complexes. The right intraventricular tracings show an initial positive deflection, the S-T elevation may be due to pressure injury.

the V leads. There was a marked decrease in the amplitude of the complexes when the catheter was withdrawn from the cavity of the left ventricle (fig. 9). The value of this change in potential in the accurate localization of the tip

Sensitivity of the Ventricular Endocardium. The endocardium of the ventricles is more sensitive to mechanical stimulation than that of the atria. Clinically, premature beats and ectopic rhythms occur more frequently when the

ventricular endocardium is disturbed during catheterization. In dog experiments, the atrial endocardium can be abraded without the appearance of arrhythmias. In studies of the effect of endocardial injury in dogs, Hellerstein and Katz[6] noted the sensitivity of the ventricular endocardium and also noted that the upper part of the ventricular septum and the tips of tricular cavity, in the region of the upper part of the septum (figs. 9 and 10). In several patients runs of ventricular beats occurred for 2 to 4 seconds, spontaneously disappearing when the catheter was withdrawn or passed forward toward the apex. In several patients premature ventricular beats occurred only when the catheter was introduced into the apex of

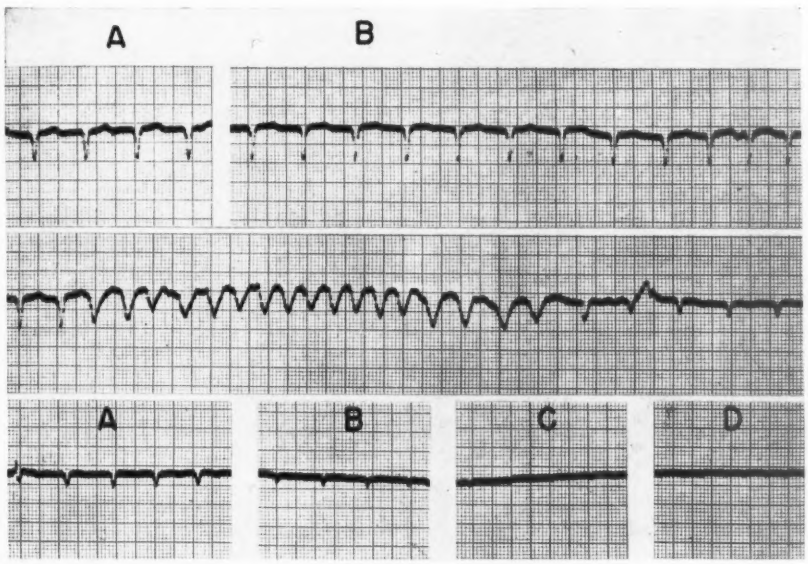

FIG. 9. Tracing taken from L. J., a white male with syphilitic aortic insufficiency without congestive failure. The curves shown here represent portions of a continuous strip recorded from the tip to the catheter as it was withdrawn from the apex of the left ventricle to the left subclavian artery. The upper row, *A*, represents a control curve. Row *B* is the curve recorded as the catheter was withdrawn. The middle row is continuous with the upper row. Note the transient ventricular tachycardia (rate 250) which lasted 4.4 seconds, and was produced when the catheter tip was situated near the upper septum. Also note the marked diminution of voltage when the catheter tip enters the root of the aorta. Curve *A* on the bottom row was taken from the ascending aorta, curve *B* from the arch of the aorta, and curve *C* was taken from the left subclavian artery. This series of tracings demonstrates the irritability of the upper septum and the change in voltage as the cathether is withdrawn from the ventricle. All curves were taken at N/3 sensitivity.

the papillary muscles are extremely irritable, giving rise to runs of ventricular beats, and occasionally to ventricular tachycardia.

In our experience with right heart catheterization, premature ventricular beats were noted at one time or another during the procedure in all patients. Ordinarily slight movement of the catheter will eliminate the disorder. Premature beats were most frequently produced when the catheter first entered the left ventricle. The number of premature beats spontaneously decreased without moving the catheter. This apparent acclimatization of the endocardium to an indwelling catheter has been noted also in the right side. It is possible that the catheter may shift from an irritable focus due to respiration or to the heart beat.

Form of the Premature Ventricular Beats. In the intraventricular tracings, premature beats were of the QS variety, when recorded in the

ventricle from which they arose. The ST-T area was positive (fig. 7). When the premature beats originated in the right ventricle, the form of the QRS complexes in the limb leads resembled that

electrode is situated above the atrioventricular orifices, tracings recorded here reflect intracavitary potentials.[10] Generally, aV_R tracings are negative, as are the intracavitary leads.

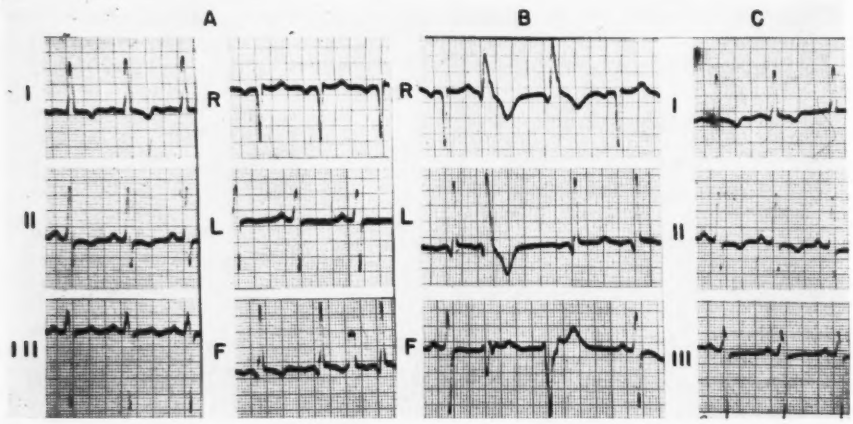

FIG. 10. Tracings taken from C. W., a Negro man with syphilitic aortic insufficiency and congestive heart failure. Shown under *A* is a control record taken shortly before catheterization of the left ventricle. Curves under *B* are augmented limb leads and show multiple premature ventricular beats when the catheter was inserted into the apex of the left ventricle. Curves under *C*, taken 5 minutes later than those in *B*, show the spontaneous disappearance of the premature beats. Discussed in the text.

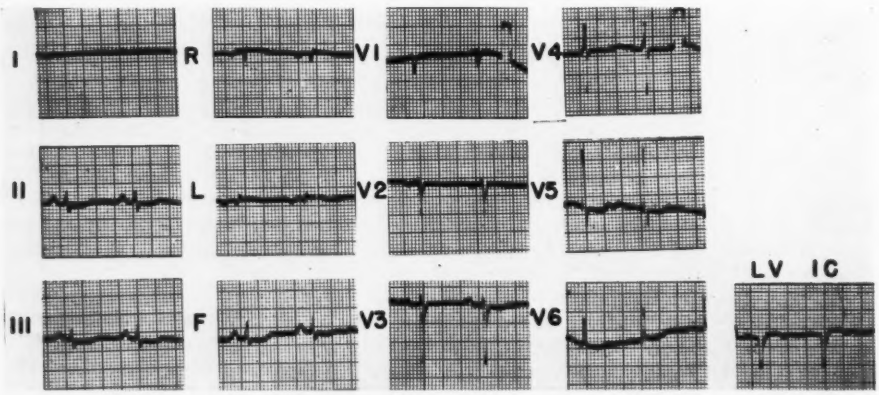

FIG. 11. Curves taken during pneumonectomy on K. W., a white male. The intraventricular curve was secured by passing a catheter through a left pulmonary vein. The intraventricular tracing taken at N/5 sensitivity shows a QS complex with elevated S-T segment.

of left bundle branch block and when they arose in the left ventricle, right bundle branch block (fig. 10).

Relation of "Unipolar" Right Arm Lead to Intraventricular Leads. It has frequently been assumed that because the right arm exploring

However, this relationship may be affected by changes in the electrical and anatomic position of the heart. For example, in figure 1, the heart is rotated to the left, electrically. The net value of the right arm lead is positive, although the cavity leads are negative. In this

particular patient the duration of the QRS complex is prolonged (0.12 second). The tall delayed R wave in lead aV_R resembles that found in right bundle branch block. However, the configuration of the precordial leads and the absence of a large R wave in the right cavity tracing makes the diagnosis of right bundle branch unlikely.

At the present time, therefore, it is probably safe to state that the right arm lead reflects intracavitary potentials only when it is in a negative field and when the intraventricular conduction is normal. A net positive value of a right arm lead may occur in abnormal intraventricular conduction, or with rotation of the heart.[11] In the latter instance, any lead which is in a negative field would reflect the net electrical potentials of the ventricles better than the right arm lead. In our cases, the right arm lead resembled the intracavitary leads only when the right arm lead had a net negative value. Therefore one cannot assume that the right arm lead invariably reflects intracavitary potentials.

Relation between Precordial Leads V_5 and V_6 and Leads from within the Left Ventricle. When a deflection in one direction occurs in a precordial lead (or epicardial lead) simultaneously with a deflection in the opposite direction in the cavity lead, both deflections may be attributed to forces across a boundary between active and resting muscle in the free wall of the ventricle.[8] In all our cases, the net value of the QRS complexes of the left cavity leads was negative, and of the left precordial leads, positive. In 6 of 9 patients, in V_5 and V_6 there was a small negative deflection preceding the major positive deflection, i.e., qR complexes. This negative wave is due to depolarization of the upper septum from left to right. In the other 3 patients, the complexes were of the R or Rs variety. In 8 of 9 patients, the net value of the ST-T complex of the left cavity leads was opposite in sign to that of the left precordial leads, positive and negative, respectively. The vector force producing the ST-T deviations is such that any electrode "facing" the endocardium of the free wall of the left ventricle is in a positive field (in left ventricular cavity, root of aorta) and those exploring electrodes on the other side (epicardial) will be in a negative field (V_4, V_5 and V_6). This again demonstrates the importance of the spatial orientation of the exploring electrode to an altered area of repolarization.[6, 12]

Relation between Right Precordial Leads (V_1 and V_2 and Intraventricular Leads. In 8 of 9 patients, the right precordial leads had ST-T complexes which had positive net values and showed S-T segment elevation, similar to that in the left intracavitary leads. Furthermore, in leads from the right ventricular cavity and right precordium, the ST-T complexes had net positive values in 3 cases, and in 2, they were positive in the precordial lead, and negative in the right intraventricular lead. The similarity of the RS-T complexes in the right precordial and left intracavitary leads, the concordant displacement of the S-T segment in both right precordial and right intraventricular leads indicated that the form of the RS-T complex was determined to a great extent by forces produced by repolarization of the septum and the free wall of the hypertrophied left ventricle. In the 2 patients with oppositely directed RS-T complexes, one may assume an earlier repolarization of the subepicardial lamina of the free wall of the right ventricle.[8]

Summary and Conclusions

1. The intracavity potentials of the human left ventricle have been studied in 8 patients by the technic of retrograde ulnar arterial catheterization, and in one patient by passing an electrode into the left ventricle through a pulmonary vein at the time of operation for pneumonectomy.

2. In the region of the upper part of the interventricular septum, curves from the right ventricle showed a small R wave and a deep S wave; in the corresponding region of the left ventricle, the complex was of the QS variety. This consistent finding is interpreted to be confirmatory of Wilson's concept of the earlier depolarization of the upper interventricular septum from left to right.

3. In one patient, a tracing from the apex of the left ventricle showed a definite positive deflection, and a deep S wave (rS). The origin of this positive deflection is obscure.

4. In 8 of 9 cases, the direction of the RS-T complex of the cavity leads of the left ventricle was opposite to that in the lateral left precordial leads, indicating that the RS-T deviation was produced by forces in the free wall of the hypertrophied left ventricle.

5. That the right arm "unipolar" limb lead may not reflect cavity potentials is demonstrated in one case which had negative intraventricular leads, and a positive right arm lead.

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The Effect of Posture and of Compression of the Neck on Excretion of Electrolytes and Glomerular Filtration: Furthur Studies

By W. N. Viar, M.D., B. B. Oliver, M.D., Seymour Eisenberg, M.D., T. A. Lombardo, M.D., Kathryn Willis, M.D., and T. R. Harrison, M.D.

Compression of the neck of the sitting subject caused increase in urinary sodium output without change in glomerular filtration (creatinine clearance) or apparent cardiac output (electrokymograph). The possible existence of an intracranial mechanism sensitive to alterations in volume of extracellular fluid and regulating the volume of extracellular fluid is suggested.

PREVIOUS studies from this laboratory,[1, 2] have indicated: (a) that under comparable conditions the urinary excretion of sodium, like that of chloride[3] and of water,[4] is less in the sitting than in the recumbent position, and (b) that compression of the neck of the sitting subject may cause increase in sodium excretion. Since renal clearances were not measured, the previous work provided no evidence concerning the relative importance of alterations in filtration and in reabsorption.

The purposes of the present communication are to extend the previous observations, particularly in relation to: (a) investigations of glomerular filtration and cardiac output, (b) studies of the excretion of chloride and of potassium, as well as of sodium and water, and (c) measurements during congestion of the head under different circumstances (induced by tilting the body or by compression of the neck of the recumbent subject). It is hoped that such observations may furnish information concerning some of the mechanisms regulating sodium excretion under physiologic conditions, in order that these mechanisms may later be investigated in patients with circulatory disorders.

Methods

The subjects were normal males, aged 22 to 30. Various attempts were made to maintain constancy of sodium excretion by previous regulation of either the intake of "added" sodium only, or by utilizing a diet of known sodium content and also measuring the "added" sodium. None of the various plans employed resulted in a high degree of constancy of diurnal and nocturnal sodium output. The least unsatisfactory procedure involved the utilization of a diet containing 1 Gm. of sodium, plus the addition of 7.0 Gm. of sodium chloride to the food at the regular meals (2 Gm. at breakfast and 2.5 Gm. at the other two meals). Even with this procedure, considerable variations of sodium output occurred. Such variations are probably to be ascribed to incidental alterations in activity, posture, endocrine balance, environmental temperature, and other factors.

On the date of the experiments the subject came to the laboratory without breakfast, and ate no food other than one-half of a chocolate bar every hour or one egg every two hours until the termination of the experimental procedure which lasted 6 to 12 hours (usually 10). In an attempt to attain reasonable constancy of urine volume and of sodium excretion, 200 ml. of a loading solution of hypotonic (0.14 per cent) sodium chloride were ingested at hourly or half hourly intervals. However, these functions varied widely in the different subjects, and they displayed unexplained hourly variation in the same subject. Of the several different variations employed in the loading procedures, the least unsatisfactory appeared to be the ingestion of the solution at hourly intervals in the recumbent position and at

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half hourly intervals in the sitting posture. It was also found that, under the conditions of the experiments, even approximate constancy of excretion of sodium and water was not minimum. However, it was found that this technic was highly unsatisfactory because the sitting subjects often displayed an initially positive sodium balance during the procedure

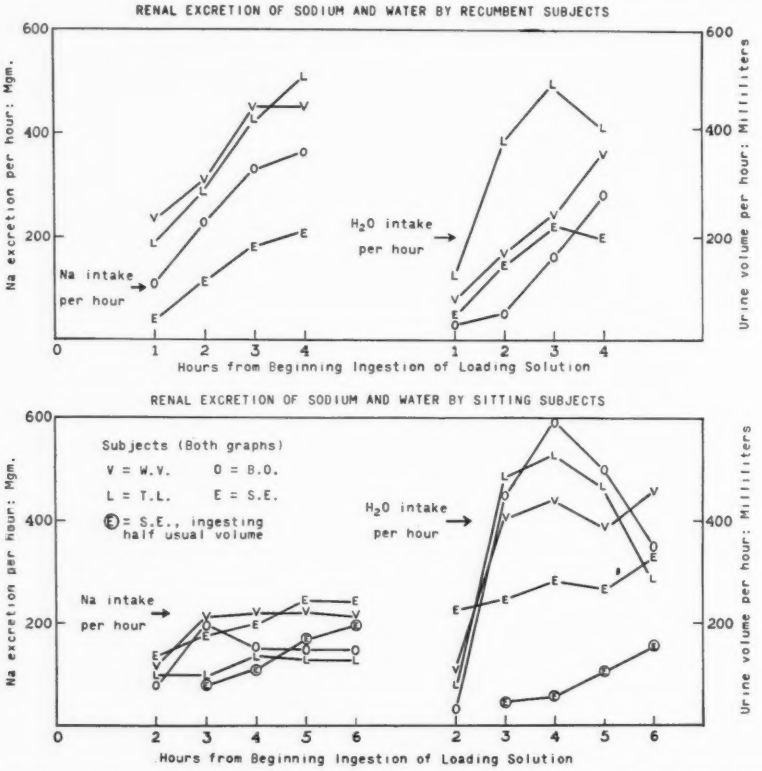

FIG. 1. The upper graphs indicate the inconstancy of the output of sodium and water during the initial hours and the lesser degree of variability after the third hour under the conditions of the experiment (ingesting 200 ml. of 0.14 per cent sodium chloride solution every hour in the recumbent posture).

The lower graphs display similar findings for the sitting posture when twice as much of the same loading solution was ingested. When the same amount was ingested as in the recumbent position (the experiment indicated by an encircled E) the excretion of both sodium and water continued to increase during the entire six hour period.

Despite the lesser intake of sodium in the recumbent posture the usual negative sodium balance and the usual increase in excretion (as compared with that occurring in the same subjects when sitting) was encountered in this position.

attained until after two or more hours of loading had passed (fig. 1).

In the earlier experiments a given individual was studied on successive days in the hope that incidental variations in sodium excretion (due to alterations in activity, environmental temperature, etc.) might thereby be kept at a minimum. However, it was found that this technic was highly unsatisfactory because the sitting subjects often displayed an initially positive sodium balance during the procedure and the recumbent subjects exhibited a markedly negative sodium balance (fig. 2), which altered the results of the subsequent days. Therefore, the procedure of allowing two or more days to elapse between successive experiments on the same subject was adopted for the later experiments.

(a) *Sodium* was measured by the method described by Hoffman and Osgood,[5] with the slight modifications mentioned in the previous study.[2]

(b) *Potassium* determinations were done by the chloroplatinic acid titrimetric method. The method of Consolazio and Talbott[6] was utilized as described, with the exception of the use of 1 and 2 ml. urine samples rather than 0.2 ml. samples. By this alteration in technic, a sample containing 0.0008 mEq. or more was assured, thus obviating the 10 to 20 per cent recovery loss produced by the use of samples containing less potassium.[7]

(c) *Chloride* was determined by a modification of the Volhard-Harvey[8] open Carius titrimetric method.

(d) *Creatinine.* Endogenous creatinine clearance was determined by the Bonsnes and Taussky[9] modification of the Jaffe reaction, utilizing the modified Folin-Wu tungstic acid method of protein precipitation advocated by Brod and Sirota.[10] It should be pointed out that a correction in technic was effected early in the course of these experiments which led to somewhat higher clearance values. The order of magnitude of the change was quite small, and did not affect the values on a given day.

(e) *Cardiac output.* Directional changes in cardiac output were measured by the electrokymographic technic as described by Ring and co-workers,[11] with certain modifications which will be discussed in detail elsewhere.[12] It should be pointed out that regardless of the absolute accuracy of this procedure, it apparently furnishes a reliable index of directional changes.

Results

In the various figures and tables the findings in those experiments which yielded positive results are presented in some detail, while the negative results are presented in summarized form.

1. *Electrolyte Excretion, Glomerular Filtration and Cardiac Output in the Recumbent and Sitting Postures.* The data on glomerular filtration and electrolyte excretion are presented in table 1. The urine volume was relatively greater (in comparison to the water intake) in the recumbent posture. Although the sodium intake was twice as great in the sitting as in the recumbent posture, the output of sodium was greater in the latter position (table 1, figs. 1 and 2). It is evident that the excretion of chloride tended to parallel that of sodium which, as previously reported,[1, 2] tends to be markedly less in the sitting than in the recumbent position.

Potassium excretion displayed no consistent variations with posture (table 1, fig. 2). In both positions the urinary potassium exhibited a decline after the first four or five hours of in-

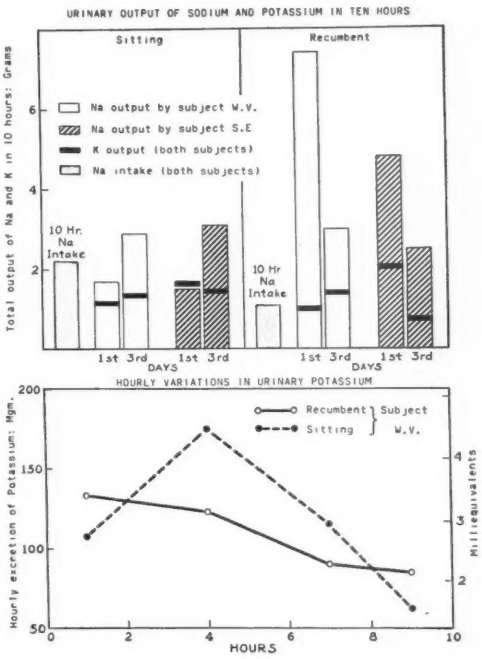

FIG. 2. The subjects ingested the loading solution (0.14 per cent sodium chloride) in amounts of 400 (sitting) or 200 (recumbent) ml. per hour for a 10 hour period. In the upper graph the urinary output of sodium (columns) and potassium (bars) during this period is depicted for the first and last of three successive days of loading. The values for the second day, which were intermediate in all instances, are not shown.

In both subjects the sodium balance was positive in the sitting position during the first day's experiment but negative on the third day, indicating that the previously retained sodium was now being excreted. When, after a 10 day interval, the procedure was repeated with the subjects in the recumbent position, the initial day's sodium balance was markedly negative and this excessive excretion of sodium was still present, but in much lesser degree, on the third day.

In contrast to sodium the excretion of potassium did not display consistent alterations either as the result of changes in posture or of continuing the procedure for three successive days.

In the lower graph are shown data on the hourly excretion of potassium in the two postures. The initial rise in potassium excretion was inconstant but the later decline was a consistent finding in most of the experiments.

TABLE 1.—*Electrolyte Excretion and Creatinine Clearance in the Sitting and Recumbent Postures.*

Subject	Position	Date 1949	Hour of Ingestion	Creatinine Clearance	Urine Volume per hr.	Electrolyte Excretion		
						Na mEq.	Cl mEq.	K mEq.
				ml. per min.	*ml.*	*per hr.*	*per hr.*	*per hr.*
B. O.	Recumbent	9/26	3	109	164	14.6	13.3	—
			4	104	291	16.0	14.6	2.32
		10/4	3	139	209	19.5	17.8	—
			4	132	390	19.8	18.8	6.02
	Sitting	11/15	3	141	455	8.6	11.8	—
			4	129	545	7.2	—	4.065
		11/19	3	115	272	7.6	—	—
			4	117	574	10.9	—	5.53
T. L.	Recumbent	9/28	3	109	490	18.1	20.5	—
			4	106	400	22.6	25.5	4.55
		10/4	3	113	192	7.4	6.5	—
			4	104	275	7.7	6.6	1.43
	Sitting	11/15	3	119	490	4.1	6.66	—
			4	119	486	6.7	—	5.24
		11/19	3	113	365	5.6	—	—
			4	103	286	7.0	—	2.30
W. V.	Recumbent	9/29	3	131	261	19.9	21.0	—
			4	127	362	20.3	19.9	5.25
		10/5	3	136	142	28.2	15.2	—
			4	131	355	17.5	16.8	3.55
	Sitting	11/16	3	155	406	9.0	16.96	—
			4	152	437	9.4	—	4.76
		11/20	3	141	319	6.0	—	—
			4	143	506	7.3	—	3.84
S. E.	Recumbent	9/29	3	107	236	7.6	9.5	—
			4	109	192	9.4	11.7	3.34
		10/5	3	114	246	11.4	12.1	—
			4	114	302	14.2	14.1	4.41
	Sitting	11/16	3	144	252	5.8	8.69	—
			4	145	289	7.0	—	4.90
		11/21	3	124	181	7.1	—	—
			4	111	316	8.8	—	3.51

The subjects drank 200 ml. of 0.14 per cent sodium chloride solution hourly when recumbent and half hourly when sitting. The data shown are for the third and fourth hours after starting to ingest this loading solution.

TABLE 2.—*Effect of Compression of the Neck of Sitting Subjects on Creatinine Clearance and on Renal Excretion of Sodium.*

Subject	Conditions	Creatinine Clearance (ml. per min.)							Sodium Excretion (mg. per hr.)						
		Before*	During (hrs.)				After (hrs.)		Before*	During (hrs.)				After (hrs.)	
			1	2	3	4	1	2		1	2	3	4	1	2
B. O.	Control	117	103	111	112	111	108	107	198	165	159	157	166	213	168
	Neck compressed	132	131	129	123	119	118	125	189	210	260	261	255	180	173
T. L.	Control	119	143	115	108	109	143	111	93	154	150	138	123	174	135
	Neck compressed	122	122	125	110	124	107	95	179	219	229	264	224	167	140
S. E.	Control	145	139	145	144	147	145	147	161	191	243	237	261	259	411
	Neck compressed	111	112	112	111	106	114	112	225	250	280	270	252	200	207
W. V.	Control	141	143	133	138	141	138	137	206	216	226	214	270	237	255
	Neck compressed	124	133	131	132	127	128	125	170	220	283	268	271	139	130

* The third hour of ingesting the loading solution and the hour immediately preceding compression of the neck.

gesting the potassium-free loading solution (fig. 2).

As judged by creatinine clearance, glomerular filtration exhibited rather wide and unexplained variations in the same subject on different days, but tended to remain relatively constant in a given individual on a given day. Consistent differences between sitting and recumbent values were not encountered. The average values were somewhat greater in the sitting subjects. This difference was probably the result of slight changes in analytic technic. It is evident from these studies and from those of others,[3] who have found minimal or no difference between the two positions, that the marked variations in sodium excretion must be ascribed to alterations in tubular activity and not to changes in filtration.

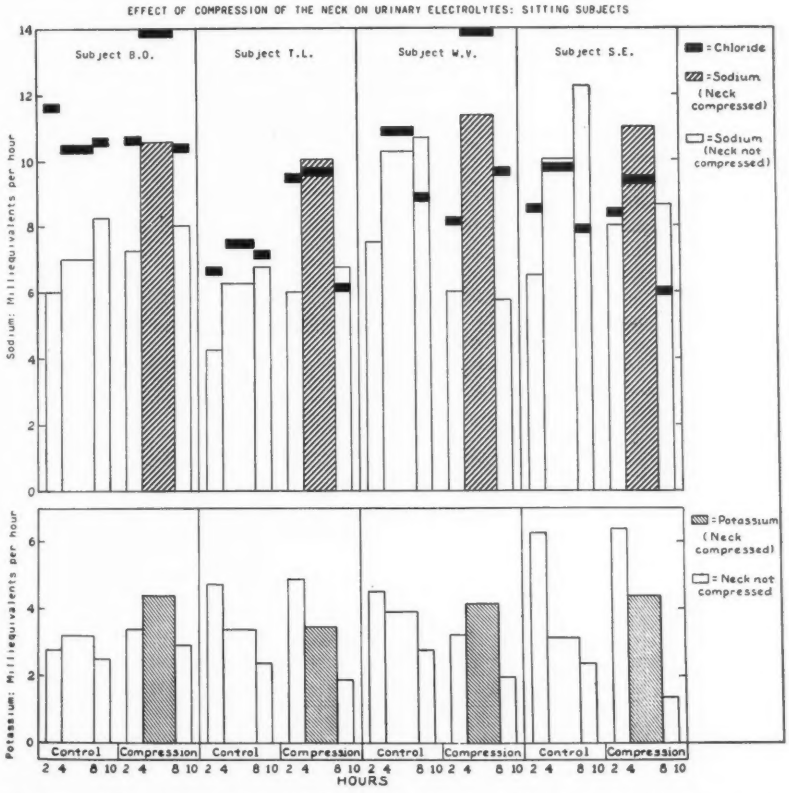

FIG. 3. The sitting subjects ingested the usual loading solution for a period of 10 hours during the last eight of which hourly urine specimens were obtained.

During the control studies (white columns) sodium excretion tended to rise and potassium excretion to fall. When the experiments were repeated and the neck was compressed for four hours (shaded columns) during the middle of the eight hour period, sodium excretion increased in each instance over that immediately before and after and also over that which occurred during the corresponding period in the control experiments. Chloride excretion behaved similarly. Potassium excretion seemed to be slightly increased during compression of the neck in 2 of the subjects but not in the other 2.

The effects of posture on directional changes in cardiac output were studied also. These observations will be published in detail elsewhere.[12] Cardiac output exhibited the usual decline in the sitting posture, as previously found by others[13, 14] using different methods. The average of two or three cardiac output determinations was obtained in the recumbent

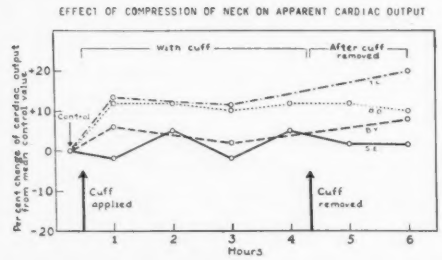

FIG. 4. Effect of compression of the neck on cardiac output. The subjects assumed the sitting position and drank 200 ml. of 0.14 per cent sodium chloride solution every 30 minutes for 10 hours. Cardiac output was measured at the third and fourth hours. The cuff was applied about the neck and inflated to 20 mm. Hg and cardiac output measured hourly for the subsequent 4 hours. The cuff was then released and cardiac output measured for 2 additional hours.

The average of the first two cardiac output values was used as the control value. The cardiac output values subsequently obtained were plotted as percentage change from the control.

and in the sitting position, for each of the 4 subjects. The average of these four cardiac output values was 6.3 liters per minute in the recumbent position, and 5.8 liters per minute in the sitting position. Thus an 8 per cent decrease in cardiac output occurred in changing from the recumbent to the sitting posture.

2. *The Effect of Compression of the Neck of Sitting Subjects on Electrolyte Excretion and on Glomerular Filtration.* The data concerning sodium (table 2, fig. 3) are in accord with those previously reported, an increase being found upon the application of a pressure of 20 mm. Hg to the necks of the several subjects. Similar increments in the excretion of chloride were observed when the neck was compressed (fig. 3). On the other hand, the excretion of water was not affected significantly. Inflation of the cervical cuff produced no significant immediate changes in pulse rate or blood pressure. Hence it is unlikely that alterations in carotid sinus

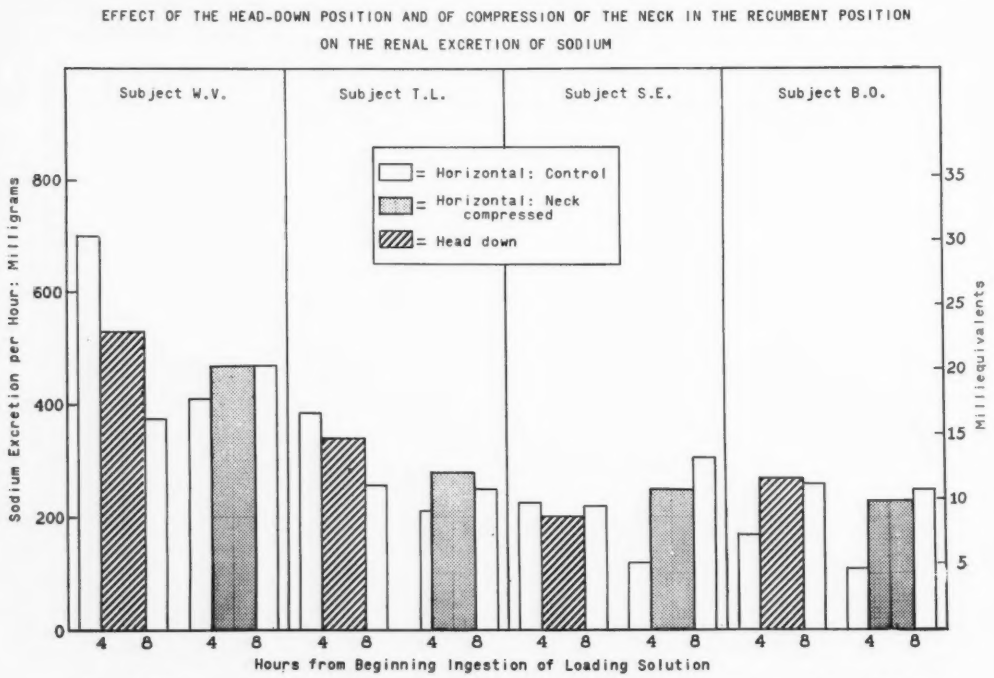

FIG. 5. The recumbent subjects ingested the standard loading solution for a period of 10 hours during the last eight of which urinary sodium was measured.

Elevation of the foot of the bed to an angle of 20 degrees for a period of four hours had no consistent effect on sodium excretion as compared with that in the preceding and succeeding two hour periods. Compression of the neck of recumbent subjects was attended by a slight rise in sodium ex-

activity were concerned in the effects on electrolyte excretion.

Consistent results as regards potassium were not obtained by compression of the neck. In 2 of the subjects urinary potassium rose, while in the other 2 the usual decrease occurred as in the control observations when the neck was not compressed. In view of the failure of cervical compression to cause a decline in potassium excretion, it seems unlikely that the increased excretion of sodium was mediated via the adrenal cortex.

Glomerular filtration (table 2) remained unaffected by compression of the neck, as did cardiac output (fig. 4). It is, therefore, clear that the observed alterations in electrolyte excretion are to be ascribed to variations in renal tubular activity, and that such variations are not to be ascribed to changes in cardiac output.

3. *The Effect of the Head-Down (Trendelenburg) Position on Sodium Excretion.* The results obtained when the foot of the bed was elevated at an angle of approximately 20 degrees are presented in figure 5. Consistent alterations in sodium excretion did not occur in the 4 subjects. Filtration rate did not change significantly in the one experiment in which it was measured. In view of the negative results, the excretions of chloride and of potassium were not measured.

4. *The Effects of Compressing the Neck of Recumbent Subjects on Sodium Excretion.* The failure of sodium excretion to increase in the head-down as compared with the horizontal position was surprising, in view of the previous observations of the effects of posture and of compressing the necks of sitting subjects. Consequently, additional experiments were performed, the neck being compressed by a pressure of 20 mm. Hg while the subject was in the recumbent posture. The results (fig. 5) of these experiments were in sharp contrast to those obtained in the sitting position (fig. 3). The rise in sodium excretion occurring upon compression of the neck in the sitting experiments was not observed in the same subjects when recumbent.

Discussion

Excretion of electrolytes is conditioned by numerous variables. To control all of them would require accurate standardization not only of dietary and of fluid intake, but also of environmental temperature, physical and psychic activity, emotional state, endocrine balance, and probably of various other as yet unknown factors which influence the activity of the homeostatic mechanisms of the body. Since such elaborate standardization has been impractical in our work, it has been necessary to determine by trial and error the experimental conditions which can be expected to yield reasonably uniform results.

The data in figures 1 and 2 indicate that a satisfactory degree of constancy of excretion of sodium and of water can be maintained for several hours, if the following conditions are fulfilled: (1) The intake of sodium in the diet should be controlled within a fairly narrow range, and a known amount of sodium chloride should be added to the food for several days prior to the actual experiments. (2) Observations should not be made on the same subject on successive days, as the sodium balance of the initial day (markedly negative when recumbent and usually positive when sitting) may have a striking influence on excretion of sodium on the subsequent days (fig. 2). (3) The experiments should preferably be started in the basal state, and only minimal amounts of food (of constant sodium content) should be ingested during the experiments. (4) Data are not available with various loading solutions but when the solution employed in these experiments (0.14 per cent sodium chloride solution) is ingested in the amounts indicated (200 ml. hourly and half hourly, respectively, for recumbent and sitting postures), the output of water and of sodium rises rapidly for a period of two to three hours, and then maintains reasonable constancy or changes slowly for several additional hours (fig. 1). Hence if one wishes to have a preliminary control period before an experimental procedure, it is necessary that the third or, preferably, the fourth hour after the onset of loading be considered

cretion, but the postcompression control period exhibited still further rise. The order of magnitude of these changes is not considered significant.

as the control period. Even when these several precautions are observed, striking constancy of results cannot be expected. Thus, under the conditions described, the subject often tends to have, after the first few hours of loading, an initially positive sodium balance when sitting (figs. 1 and 3) and an initially negative balance when recumbent (figs. 1 and 5), these alterations often being followed by gradual increase and decrease, respectively, in the sodium output during the later hours of prolonged experiments. Likewise, the hourly sodium and chloride outputs vary from day to day, and the potassium excretion may undergo an initial rise (during the early hours of loading), usually exhibiting a steady decline during subsequent hours (fig. 2).

The data may clarify somewhat the relative quantitative importance of some of the several factors determining sodium output. Over a period of 8 to 12 hours, the posture of the subject was a more important factor than was the current intake of sodium. Thus the recumbent subjects who were ingesting only one half as much sodium excreted much more than did the sitting subjects (figs. 1 and 2, table 1). On the other hand, the degree of saturation of the sodium stores of the body, i.e., the sodium balance during the several preceding days, was more important than posture. Thus, when the procedure was repeated daily in the same posture, the striking difference between sodium excretion during the initial day spent in two positions had disappeared by the third day, as the result of respective accumulation and depletion in the sitting and recumbent postures (fig. 2).

Mechanism of Postural Effect on Urine Volume. Brunn and his co-workers[4] have presented convincing evidence that the decline in urine volume in the standing position is related to increased activity of the antidiuretic hormone of the posterior pituitary. When allowance is made for the time lag in the action of this hormone,[15] it would appear that it is released as the result of a rapidly acting mechanism—probably situated in the hypothalamus. It appears likely that the hypothalamic-posterior pituitary mechanism is concerned also in producing the relative oliguria of the sitting position.

The data in figure 1 indicate that in both postures the urine volume tended to increase during the first several hours of the experiments, and became maximal three to four hours after the subjects began to ingest the hypotonic loading solution. It is also evident, from figure 1, that during this period the water load (i.e., the amount of retained water) was increasing more rapidly than was the sodium load (amount of retained sodium), and hence that there was a tendency toward decline in osmotic pressure of extracellular fluid. Since the hypothalamic-posterior pituitary mechanism is very sensitive to slight changes in osmotic pressure,[15] this disproportion would tend to reduce the activity of the mechanism responsible for water retention.

Compression of the neck had no consistent effect on urine volume.

Mechanism of Postural Changes in Sodium Excretion. During the past several years considerable difference of opinion has existed concerning the relative importance of filtration and of reabsorption in relation to alterations of sodium excretion. The observations of the present study indicate that the changes of sodium excretion induced in healthy subjects by change in posture and by compression of the neck are independent of filtration, and hence must be attributed to alterations in tubular activity.

The suggestion that changes in cardiac output constitute a major controlling factor in determining sodium excretion is not supported by these studies. The sodium output of the sitting subject could be increased either by lying down, which caused an increase in cardiac output, or by compression of the neck, which caused no increase (fig. 4).

Compression of the neck by the cuff was not attended by significant immediate changes in blood pressure or pulse rate. It therefore seems unlikely that alterations in the activity of the carotid sinus mechanism were responsible for the effects of cervical compression on sodium excretion.

It is of interest to note that the decline in sodium excretion in the sitting as compared

with the recumbent posture (table 1) was greater than the increase produced by compression of the neck of sitting subjects (table 2). In other words, the latter procedure was only partially effective in overcoming the decline produced by the sitting posture. Since it has been shown that venous congestion of the legs causes decline in sodium excretion,[16] and since the sitting position tends to produce such congestion, this is one possible factor. Another is the increase in renal venous pressure, which has been shown to decrease sodium excretion,[17] and which would be expected to be present in the sitting as compared to the recumbent posture. However, compression of the neck which caused increased excretion of sodium, could have no direct effect on the degree of congestion of the legs or on the level of renal venous pressure. Hence it would appear that some effect on the intracranial contents is probably also concerned in the postural changes in sodium excretion.

If the tentative conclusion is drawn that the increase in sodium excretion produced by compression of the neck of sitting subjects is the result of some alterations within the cranial cavity, and that the same mechanism constitutes one factor in the decline in sodium excretion produced by the sitting position, the question arises as to the precise nature of the mechanism involved. On first thought, it might appear that sodium excretion tends to parallel intracranial venous pressure, which is diminished by the sitting posture and increased by compression of the neck. The decline in sodium excretion, in states of peripheral circulatory failure which are usually accompanied by decline in venous pressure, is in keeping with such an assumption. On the other hand, heart failure is accompanied by elevation of venous pressure and by decline in sodium excretion. Likewise, intravenous administration of hypertonic albumin solution causes rise in venous pressure[18] but decline in sodium excretion.[19] It seems unlikely, therefore, that alterations in intracranial venous pressure are directly concerned in the regulation of sodium excretion.

Cerebral blood flow was not measured in these experiments, and the possibility that alterations in this function may have been concerned in the effects on sodium excretion cannot be entirely excluded. This possibility involves, however, the unlikely assumption that compression of the neck and shift to the horizontal posture cause the same directional changes in cerebral blood flow.

The observations on the effects of posture and of compression of the neck are compatible with the concept of an intracranial "volume center," activated by decline in the volume of fluid (blood or extravascular) in the cranial cavity, and functioning in such a way as to tend to maintain constancy of the volume of body fluids. Such a concept is in accord with the retention of sodium in states of peripheral circulatory failure. The retention of sodium in patients with heart failure is not contrary to this concept, because heart failure is initially associated with redistribution of blood to the central portions of the vascular bed, i.e., to the heart and lungs.[20, 21] Such redistribution will necessarily be attended, in the initial stages, by deficit of blood and extravascular fluid in the periphery (and, presumably, in the cranial cavity). Unfortunately, there are no methods of measuring fluid volumes in the cranial cavity, and in the absence of such measurements this concept can be supported only by indirect evidence.

If an intracranial mechanism regulating volume of body fluids actually exists, the data reported in this paper, and the studies of others,[19] offer certain indications concerning its function.

(1) The reason for the discrepancy between the effects of compression of the neck in recumbent subjects, and in the same subjects when sitting, is not clear and requires further investigation.

(2) In determining the level of sodium output other factors, such as the previous intake of sodium, are of greater quantitative importance than posture and compression of the neck, which appear to act through the assumed central mechanism. The latter would, therefore, appear to be analogous to the fine adjustment of a microscope, the coarse adjustment cor-

responding to such factors as the sodium stores of the body and the endocrine balance.

(3) If it is assumed that the changes in sodium excretion were conditioned, in some manner, by changes in intracranial fluid volume, the question arises as to whether alteration in the amount of blood or of extravascular fluid was responsible. In order to distinguish between these possibilities it would be necessary to establish conditions in which the intravascular and extravascular fluid volumes varied in opposite directions. Such was not done in our experiments, but has been done by others[19] who found that the injection of hypertonic albumin solution caused decline in the excretion of sodium but not of water. Since, following the administration of hypertonic albumin solution, the intravascular volume would be expected to increase at the expense of the extravascular volume, this observation, when considered in relation to our findings, suggests that decline in extravascular fluid volume (or some closely related factor) within the cranial cavity causes reduction in sodium excretion. The fact that potassium, a predominantly intracellular ion, did not exhibit the consistent changes observed with sodium, might be interpreted as indicating that the postulated volume regulating the mechanism is related to changes in the volume of extracellular rather than of intracellular fluid in the cranial cavity.

The observations throw no light on the intermediate mechanisms whereby the postulated central mechanism might affect the reabsorption of sodium by the renal tubules. The data in the previous[2] and the present studies (table 2) indicate that the alterations in sodium output produced by changes in posture and by cranial compression develop relatively slowly, being greater in the second and third hours than in the first. On the other hand, the reduction in sodium excretion following removal of pressure from the neck appeared rapidly, and was pronounced during the first hour (table 2). These effects are perhaps suggestive of a chemical or neurochemical mechanism. They appear to be more rapid than might be anticipated if the adrenal cortex were concerned. The failure to demonstrate an inverse relationship between the excretion of potassium and of sodium is also against the assumption that the changes in sodium excretion were mediated through the adrenal gland. Observations on patients with Addison's disease and with Simmonds' disease may be of value in elucidating the intermediate mechanisms. Such studies are in progress.

The starting point of this and the preceding report[2] was the desire to investigate the concept of a homeostatic mechanism concerned with sodium retention as a means of protecting the body against various types of circulatory failure.[22–24] Our studies thus far have been limited to normal subjects and are not, therefore, directly applicable to patients with circulatory failure, or to such problems as the importance of the orthopneic position in relation to edema formation. In so far as can be judged by the data on normal subjects, it would appear that a central homeostatic mechanism concerned with sodium conservation does exist, and that this mechanism is brought into play not by decline in cardiac output but rather by alterations in the distribution and volume of body fluids.

Summary

Various procedures were studied in an endeavor to secure constancy of hourly urinary excretion of sodium, chloride, and potassium. A high degree of constancy was not obtained but certain conditions were found to reduce the extent of variability. These are described.

The change from the sitting to the recumbent posture produced well marked increment of sodium and chloride excretion, but the change from recumbency to the head-down (Trendelenburg) position caused no significant increase. Compression of the neck of the sitting subjects caused increased output of sodium and chloride, but the same procedure had little or no effect in recumbent subjects. The conditions which regularly altered the excretion of sodium and of chloride did not have significant effects on the output of potassium.

Consistent alterations in creatinine clearance were not induced by procedures which caused well-marked change in the urinary excretion of sodium and of chloride.

Cardiac output, as estimated by the electrokymograph, changed in the same direction as

sodium excretion when posture was altered. The rise in sodium excretion produced by compression of the neck of sitting subjects was not associated with measurable change in cardiac output.

The suggestion is offered that there is a central mechanism which functions as a "volume center," and which tends to maintain homeostasis by increased tubular reabsorption of sodium when conditions occur which reduce the volume of intracranial extracellular fluid.

The experiments offer no support to the concept that decline in cardiac output is of importance in relation to sodium retention. In so far as can be judged from observations on healthy subjects, the data suggest that homeostatic retention of sodium should not be ascribed to alterations in blood flow unless alterations in the distribution of body fluids can be eliminated as causative mechanisms.

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Studies on the Relation of Diet, Cholesterol and Atheroma in Chickens

By JOHN E. PETERSON, M.D., AND ALBERT E. HIRST, M.D.

In this study cockerels were fed varying diets supplemented with lard, vegetable oil, and cholesterol. The degree of atherosclerosis was compared in serial autopsies and only the cholesterol-fed group showed a significant difference. During a period of two years there was no apparent change in the degree of atheroma when the diet was supplemented with cottonseed oil or lard. Reversibility of the cholesterol-induced atheroma was also studied in a few chickens, and it appears that the early lesions may undergo considerable regression after cholesterol feeding is stopped. Older lesions, on the other hand, appear to be quite fixed.

THE SPONTANEOUS development of atherosclerosis in domestic chickens is well recognized and the vascular lesions have been compared closely with atheromatous changes in man.[1] The significance of such lesions, occurring spontaneously and after cholesterol feeding in an omnivorous animal such as the chicken, has been emphasized by Dauber and Katz.[2]

Though both rabbits and fowl appear to develop atheromatosis more readily when the added cholesterol is dissolved in some oil, it has been shown in chickens that cottonseed oil alone will not produce such lesions.[3] While the atheroma-producing effects of various diets have been attributed to some slight cholesterol content, it is now known that in rabbits the feeding of a protein diet free or almost free from cholesterol will result rapidly in vascular changes of the atherosclerotic type.[4] Atherosclerosis following the injection of colloidal solutions of macromolecular carbohydrates also has been reported by Hueper.[5]

With the above observations in mind, the authors became interested in studying the effects of long term feeding of fat from plant and animal origin. Lard was chosen for the animal fat because of its low cholesterol content. The results of these feeding programs are compared with the findings in chickens fed cholesterol and with those on a standard diet of mash.

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Anitschkow[6] and others have reported the regression of atheromatous lesions in the aorta of rabbits. A second phase of this report deals briefly with this aspect.

PROCEDURE

For this study 100 healthy-appearing white Leghorn cockerels were picked from the large stock of a commercial grower. The birds, when selected, were 10 weeks old and of similar size and weight. The 100 were divided into four groups, and each group was kept in a standard cage on wire. Fresh water was always available, and only the diet of each group was different.

The first group of 25 chickens (group A) served as a control and was fed a standard mash* ad libitum. Fresh feed was provided each day. The amount consumed was carefully measured by weighing the residue from the previous day before discarding it and adding fresh mash.

A second group of 25 (group B) was fed similarly except that a vegetable oil (chiefly cottonseed) was added to the standard mash. This feed was prepared freshly each day by thoroughly mixing a pint of oil with five pounds of dry mash—a mixture of approximately 20 per cent volume by weight.

* Globe Mills Battery Mash: 20% protein, containing ground corn 600, wheat bran 500, soya bean meal 300, ground wheat 300, ground milo 300, fish meal 200, condensed fish solubles 200, alfalfa meal 200, wheat midlings 200, meat scraps 100, fortified whey solids 50, lime stone meal 50, iodized salt 15, fortified feeding oil (1000 A–400 D),[6] manganese sulfate .375.

A third group of 25 (group C) was fed in a manner similar to groups A and B except that a pint of lard instead of vegetable oil was added to each five pounds of dry mash.

Feed for the fourth group (group D) was prepared in the same way as for group B except that 2 Gm. of crystalline cholesterol was added for each 100 Gm. of dry mash fed. The cholesterol was first dissolved in the vegetable oil then this solution was thoroughly mixed with the mash.

Results

As shown in table 1, there is little difference in the amount of atheroma found in the first three groups (groups A, B, and C). However, as expected from previous studies,[3] there was severe and extensive atherosclerosis in all the birds kept on the cholesterol ration (group D). A grading system was used for the gross lesions so that "plus 1" signifies no more than a lipoidal streak or a tiny plaque measuring not more than 5 mm. in length—a minimal lesion.

Table 1

	Autopsy No.																	
	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.
	Date																		
	20 Jan. 1948	3 Feb. 1948	17 Feb. 1948	2 Mar. 1948	16 Mar. 1948	30 Mar. 1948	13 Apr. 1948	30 Apr. 1948	14 May 1948	1 June 1948	14 June 1948	29 June 1948	22 July 1948	5 Aug. 1948	23 Aug. 1948	3 Sept. 1948	8 Oct. 1948	11 Nov. 1948	11 Jan. 1950
A. Control mash	0	0	0	0	0	++	+	+	++	0	0	0	++	+	+	0	0		++ 0 0 0
B. Mash plus vegetable oil	0	0	++	0	++	0	0	0	++	0	0	0	++	0	0	0			++ + ++ ++
C. Mash plus lard	0	0	0	0	0	0	0 +	++	0	++	++	0	0	+	0	0			+ 0 ++ +
D. Mash plus vegetable oil & cholesterol	+++	+++	+++	+++ C	+++			+++ C					+++						

Code: +—Minimal atherosclerosis
++—Moderate
+++—Severe
C—Calcification

After 80 days on this diet, a bird from each group was sacrificed by bleeding and the organs subjected to gross and microscopic examination. Similar studies were made in the remaining birds, first at intervals of two weeks, and later at longer intervals.

As this report deals primarily with the vascular changes found, it should be noted that at autopsy the heart and aorta were promptly removed and examined for gross signs of atheromatous disease. The structures were then fixed in 10 per cent formalin and sections were made from the heart, the coronary arteries, and the abdominal aorta. Additional sections were made wherever gross lesions were found. "Plus 2" denotes an atheromatous plaque but not exceeding 15 mm. in length. A grade of "plus 3" is applied to severe atherosclerosis with multiple plaques. "C" indicates calcification.

It is noteworthy that all the lesions rated as "plus 1" or "plus 2" were found in the descending aorta just above the bifurcation. The relation between "plus 2" and "plus 3" hardly indicates the striking difference found in the cholesterol-fed birds. All these chickens in group D showed severe atherosclerosis with multiple plaques about the coronary ostia, throughout the aorta, and extending into the

larger branches. In some areas these were calcified.

It is interesting that the cholesterol-fed birds were much more irritable and combative than their fellows. They ate less food and were smaller. Dauber and Katz have shown, however, that under-feeding alone will not cause such atheromatous changes.[3] The fowl on a high fat diet (both vegetable oil and lard) had a poorer appearance than the controls. Their feathers were greasy and their combs were less red. They were a little more irritable, especially in hot weather; but the gross and microscopic appearance of their organs was not significantly different.

TABLE 2

	Autopsy No.						
	13.	14.	15.	16.	17.	18.	19.
	Date						
	22 July 1948	5 Aug. 1948	23 Aug. 1948	3 Sept. 1948	8 Oct. 1948	11 Nov. 1948	19 Jan. 1950
E. Mash 30% underfed	+				0		+ 0 0 + ++ + + + + +
F. Off cholesterol on 23 Mar. '48, underfed since then	+	+			+		
G. Off cholesterol on 6 Aug. '48, normal mash since then						+++, C +++, C +++, C	

Code: +—Minimal Atherosclerosis
++—Moderate
+++—Severe
C—Calcification

ATTEMPTED REVERSAL OF LESIONS

After four and one-half months on this diet, well-established atherosclerosis was found uniformly in the autopsied birds that had been fed cholesterol. Three of the remaining birds were then removed from group D. They were banded and placed in a pen with a group of cockerels that were being underfed by allowing 70 per cent of the amount of standard mash fed to the control group. Their general appearance improved rapidly, and within a few weeks they could not be distinguished from others in the pen except for their identifying leg bands. Four months later one of these birds was examined, and the degree of atherosclerosis is noted in table 2 (group F).

Only some yellowish discoloration and a lipoidal streak were found in the descending aorta. No other gross evidences of atherosclerosis were found, and the heart and aorta appeared similar to those of the controls. Subsequent study of the other 2 of these 3 chickens revealed no more than minimal atherosclerosis in their aortas.

After nine months of cholesterol feeding, 3 more birds were removed from group D. These were banded and fed with the controls in group A. The general appearance of these 3 improved, though not as quickly or to the extent that it had in the preceding 3 chickens that had been removed four and one-half months earlier from the cholesterol-fed group.

Three months after withdrawing cholesterol all 3 of these birds were autopsied and the degree of atherosclerosis is shown in table 2 (group G). While the lesions may have been a little less severe than in the birds autopsied in the course of cholesterol feeding, there was

extensive atherosclerosis throughout the aorta with several calcific plaques. This appeared in striking contrast to the minimal changes found in the birds that had been earlier withdrawn from cholesterol feeding.

Discussion

Until a larger variety of fats has been tried, it would be unreasonable to conclude that no difference in the atherosclerosis of chickens follows the feeding of animal or vegetable fats. There appears, however, to be no significant difference in the amount of atheroma occurring in cockerels fed comparable amounts of cottonseed oil and lard. With the addition of crystalline cholesterol to the cottonseed oil, there is rapid development of severe atheroma and a considerable increase in the total lipids, neutral fat, and fatty acids in the liver.[7]

Whether the apparent difference in the reversibility of the cholesterol-induced atheroma of chickens is due to the age of the bird, or to underfeeding, or to the lesser exposure to cholesterol, cannot be determined from this study. In comparing a small group of similarly underfed birds with controls on a normal diet, there appeared, however, to be no significant difference in the amount of atherosclerosis found. While there was some increase in spontaneous atherosclerosis in the older birds (up to two and a half years), this difference was slight compared to the birds fed cholesterol. It seems more likely then, that reversibility is related to the duration and total amount of cholesterol feeding than to these other factors. This view corresponds with Anitschkow's interpretation of the regressive changes occurring in rabits.[6]

Summary

One hundred cockerels were fed various diets, supplemented with lard, vegetable oil, and vegetable oil with added cholesterol. The degree of atherosclerosis in these birds was compared at serial autopsies, and only the cholesterol-fed group showed a significant difference. In this latter group severe atherosclerosis developed rapidly and there was a considerable increase in the lipid content of the liver.

Observations in a small group of chickens suggest that if the feeding of excessive amounts of cholesterol is stopped in time, there may be some reversal of the atheromatous lesions. Later the regression of such lesions may be much less complete.

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Early Relief of Chest Pain by Ethyl Chloride Spray in Acute Coronary Thrombosis

Case Report

By JANET TRAVELL, M.D.

Within a few minutes after its onset, intense pain of acute myocardial infarction was abolished by briefly spraying the precordium with ethyl chloride. Prompt relief of pain did not prevent tissue necrosis, but may have ameliorated the clinical course. We infer that the stimulus for pain in acute infarction is of extremely short duration but gives rise to a secondary, self-sustaining pain cycle which may be terminated by altering the flow of nerve impulses from the skin. The case also illustrates the increased susceptibility to digitalis which develops some days after myocardial infarction.

SINCE WE[1-3] emphasized the forgotten fact[4] that blocking trigger mechanisms in the chest muscles is of value in controlling pain due to a fresh myocardial infarct, we have often been asked how soon after its onset the pain of acute coronary thrombosis can be relieved by local block therapy. We refer to procaine infiltration of trigger areas in the skeletal muscles and spraying of the overlying skin with ethyl chloride.[2, 3, 5-7] The following case report provides an answer to this question, since the patient was a physician and was able to apply this method of treatment (ethyl chloride spray) very early in the course of infarction.

CASE REPORT

W. T., aged 79 years, a physician. On Oct. 5 and 6, 1949, on three occasions, the patient noted transitory mild substernal pain on walking. He had been entirely free of chest pain since his second coronary thrombosis in May, 1945.

At about 10 p.m. on Oct. 6 (termed the second day of illness), while driving in his car, he had severe substernal pain which radiated across both sides of the chest and to the inner aspect of both elbows. He took glyceryl trinitrate (nitroglycerin) at once, and again at home 10 or 15 minutes later, without influencing the pain. He then sprayed his chest with ethyl chloride in interrupted sweeps in a hit-or-miss fashion. After one minute of spraying the pain stopped completely.

When seen by Dr. Harry Gold soon afterward, the patient was comfortable. There were no signs of heart failure. Blood pressure was 120/60, and heart rate, 60 per minute and regular. Rectal temperature was normal. A presumptive diagnosis of myocardial infarction was made. No morphine was given. The patient had been taking digitoxin, 0.2 mg. daily by mouth, for about one year and this was continued.

The patient slept soundly all night. He was awakened at about 8 a.m. by a return of the severe substernal pain with radiation to the elbows. He relieved the pain again in about one minute by spraying the front of his chest as before. Later in the morning an electrocardiogram was taken which, except for the T wave in Lead IV, resembled the last previous one, a year and a half earlier. Both tracings (fig. 1, C and 1) showed some depression of the S-T segments attributable to the digitoxin. The P-R interval was 0.24 second in both. There was no leukocytosis (white blood cells 8,200, polymorphonuclear leukocytes, 65 per cent).

When I first saw the patient (about noon of the third day of illness), moderate substernal and precordial discomfort had just reappeared. Pain was relieved promptly by ethyl chloride spray. Two exquisitely tender spots were then found in the outer part of the left pectoralis major muscle at the level of the second costochondral junction; each of these was infiltrated with about 1 cc. of 0.5 per cent procaine hydrochloride in saline. Diffuse radiation of pain throughout the precordium was produced momentarily by these injections. Another tender spot at the same level just lateral to the left sternal border was similarly infiltrated, with radiation to the parasternal region. A fourth trigger area was located on the front of the sternum just to the left of the midline, in what was judged to be the vari-

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able sternalis muscle.[3] When the needle was introduced into the myofascial tissues at this site, the pain reference matched the distribution of pain experienced at the onset of the attack.

The patient had no further chest pain until about 8 a.m. on the following day (fourth day of illness), when a continuous but mild ache developed across the upper precordium. When I saw him about an hour later, he had not bothered to use the spray. Another trigger area was found at a different site in the left pectoralis major muscle than had been injected the day before. This was similarly blocked by infiltration. There was no more chest pain at any time.

An electrocardiogram (fig. 1, 2) taken on the fifth day of illness, compared with that of the second day, showed that S-T_1 had become further depressed and a depression of S-T_2 and S-T_4 had appeared with flattening of T_1 and T_2 and inversion of T_3; the P-R interval had lengthened, from 0.24 to 0.27 second (lead II). These serial changes, although masked to some extent by the digitalis effects, together with the rise in rectal temperature to 100.5 F. and fall in blood pressure to 100/70 on the fourth and fifth days, respectively, confirmed the initial diagnosis of myocardial infarction. The blood sedimentation rate (Westergren) which was 24 mm. in one hour on the third day, was 70 mm. on the ninth day. Subsequently it showed a gradual return to normal; 50 mm. on the seventeenth, 27 mm. on the twenty-ninth, and 21 mm. on the forty-third day. Low-grade fever lasted eight days.

At no time did the patient appear critically ill. He was permitted to get up once a day and walk a short distance into the bathroom. However, on the eighth day, without any concomitant symptoms, the heart rate suddenly dropped from about 60 to 30 per minute and the rhythm became irregular. A few hours later an electrocardiogram (fig. 1, 3) showed complete auriculoventricular dissociation. The digitoxin was discontinued, and the heart rate and rhythm returned to normal in about 48 hours. An electrocardiogram (fig. 1, 4) then showed a normal rhythm with P-R interval of 0.24 second, and regression of the digitalis effect on the S-T complexes.

After 4 weeks, when the blood sedimentation rate was 27 mm., the patient was allowed more activity. He began to sit up and walk about. On the thirty-first day of the illness, he celebrated his eightieth birthday. After he had been up for several hours the resting pulse rate had risen to 100 per minute.

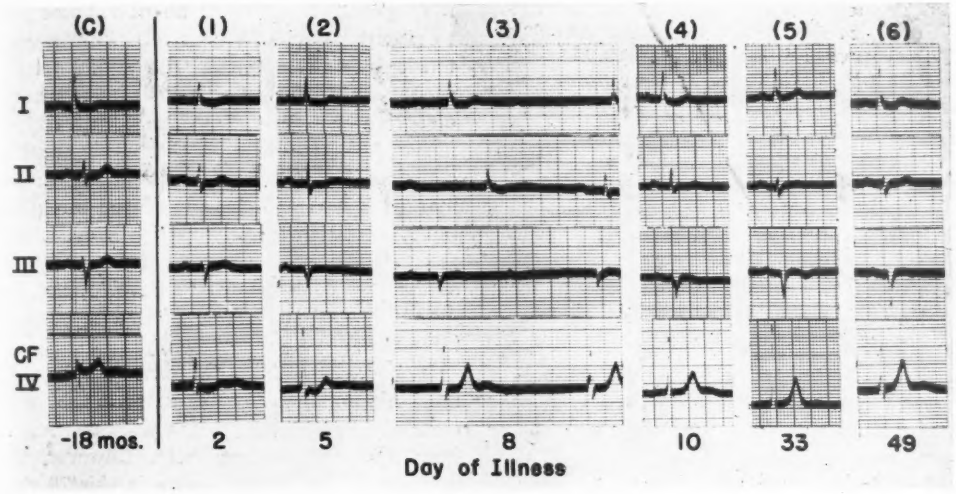

FIG. 1. Serial changes of acute myocardial infarction, on which are superimposed changes in S-T segments due to digitoxin administration and withdrawal. (C), control taken a year and a half earlier; daily maintenance dose of digitoxin, 0.2 mg. (1), (2), and (3), same daily dose of digitoxin (0.2 mg.). Note progressive intensification of digitoxin effects with complete A-V dissociation in (3) on eighth day after first appearance of chest pain. (4) and (5), no digitoxin for 2 and 15 days, respectively. Note gradual return of S-T_1, S-T_2 and S-T_4 to normal coincident with digitoxin elimination, and simultaneous deepening of S_2, inversion of T_3, and increased amplitude of T_4 as in posterior wall infarction. (6), taken 16 days after resuming digitoxin; daily maintenance dose, 0.1 mg. Some depression of S-T_1 is again evident.

It did not return to its previous level of 60 to 70 until he had rested in bed for six to seven hours. Because of this cardiac acceleration, digitoxin was resumed. A daily dose of 0.2 mg. was given for one week, and 0.1 mg. thereafter.

An electrocardiogram (fig. 1, 5) was taken on the thirty-third day, after four weeks without digitoxin. The digitalis effects had regressed; the P-R interval was still 0.24 second; notching of QRS_2 and deepening of S_2 had appeared. Another electrocardiogram (fig. 1, 6) was taken on the forty-ninth day, after 17 days of digitoxin. The flattening of T_2 in this tracing may represent a digitalis effect, but the deepening of Q_2, inversion of T_3 and increased amplitude of T_4, as compared with tracings taken during digitalization (fig. 1, C, 1 and 2) are suggestive of recent infarction of the posterior wall.

This was the patient's third attack of acute coronary thrombosis. The first occurred in April, 1943, and the second in May, 1945. Each time, unremitting chest pain had been relieved at once by procaine infiltration of trigger areas in the precordial muscles, as described under case 1 in a previous report.[2] Recovery from each attack was apparently complete, and the patient had played tennis with fair regularity, summer and winter, up to a few weeks before the third infarction. There were never any signs or symptoms of congestive failure; slight edema of the ankles was attributed to varicose veins. Arterial circulation in the extremities was excellent, although the vessel walls were of "pipe-stem" quality with some calcification on x-ray examination.

Discussion

In this case of acute myocardial infarction, intense substernal oppression with pain radiation to both elbows had been present for only 10 or 15 minutes when brief application of ethyl chloride spray to the front of the chest immediately stopped all pain. When pain recurred in 12 hours, and then 4 hours later, it again ceased at once after the chest had been sprayed intermittently during only a minute.

As a physician, the patient was familiar with the technic that we had previously described[2, 5–7] for applying ethyl chloride spray in rhythmic interrupted sweeps, which avoids frosting of the skin or aching due to excessive cold, and which often relieves skeletal muscle pain dramatically. It is difficult for most patients themselves to apply this material properly, but in this case the area to be treated, the front of the chest, was readily accessible and the patient well versed in handling the spray.

The onset of severe pain on the second day of illness probably marked the time of sudden myocardial infarction. However, the preliminary episodes of mild substernal pain suggest that thrombosis in the coronary tree and narrowing of the lumen began about 36 hours prior to closure of one of its branches. Further extension of the thrombus with additional closures may have occurred with each recurrence of severe pain on the third and fourth days of illness. It is possible that the development of complete A-V dissociation on the eighth day marked a further extension of the thrombus, but it seems more likely that this event represented increased susceptibility to digitalis action, which is known to develop, not immediately, but some time after a myocardial infarction.[8]

It should be noted in this case that the early relief of pain, almost coincident with the major closure, did not prevent signs of tissue necrosis from appearing subsequently. However, the mildness of the clinical course in this 79 year old man with a history of two previous myocardial infarcts leads one to speculate as to whether the early blocking of referred pain from the heart may not have played a beneficial role.

There is evidence to show that the discharge of high intensity impulses from a trigger area in the skeletal muscles may cause localized vasoconstriction in regions specifically related to the trigger mechanism. The regions subject to such reflex vasospasm include not only the *somatic* reference zone of pain,[6, 9, 10] which is relatively constant from person to person for a given trigger area, but probably include also specific regions of the brain, spinal cord and viscera.[11–13] Furthermore, with respect to the heart, Lindgren[14] has demonstrated that neural impulses from the superficial structures of the chest may contribute to the pain of angina pectoris. In patients with this effort syndrome, precordial local anesthesia (procaine infiltration) increased the capacity for work of cardiac

muscle as measured by exercise tolerance and anoxia tests, and hence, one may conclude, improved the coronary flow. In this patient, therefore, it seems highly possible that blocking impulses from trigger areas in the chest muscles by ethyl chloride spray contributed toward the release of vasospasm in the coronary tree. This in turn would lead to diminution in reflex ischemia surrounding the infarct and to reduction in the ultimate size of the necrotic area.

One may well ask why, when ethyl chloride spray had already relieved pain, the tender spots in the precordium were injected with procaine. This procedure was based on the concept of the latent trigger area, namely, that silent trigger mechanisms may exist with thresholds of excitability just below the critical level necessary to produce spontaneous pain. For example, at the time when this patient had no chest pain, the introduction of a needle into the latent trigger area in the sternalis muscle set off referred pain exactly like that which had attended the initiating event of cardiac infarction. Whether the discharge of subthreshold stimuli from such silent trigger mechanisms is of clinical importance cannot be stated at the present time. However, our experience with many types of painful muscle syndromes indicates that a latent trigger area may be readily activated by minor strains and stresses to produce periodically its full-blown pattern of referred pain and reflex vasomotor and other autonomic concomitants. On the basis of these observations, the logic of blocking all latent trigger areas in the chest muscles as a prophylactic measure against further coronary vasospasm is clear.

If one grants the wisdom of eradicating all possible sources of noxious stimuli under these conditions, the next question is: Could this not be accomplished equally well by repeated applications of ethyl chloride spray to the appropriate areas? The therapeutic effect of ethyl chloride spray indicates that afferent impulses from the skin play an important role in the mechanism of deep pain,[15] and that under suitable conditions altering cutaneous stimuli may relieve myofascial and visceral pain in an extraordinary manner.[5, 7, 16–18] Nevertheless, it is our impression that the latent trigger mechanism may be permanently abolished with greater certainty by direct infiltration of the trigger area itself.

Summary

Momentarily spraying the front of the chest with ethyl chloride at the onset of myocardial infarction abolished the substernal and radiating arm pain at once. When pain recurred several hours later, the procedure was again immediately effective. The latent trigger areas in the chest muscles were blocked by local procaine infiltration at a time when the patient was free of pain.

The mildness of the clinical course of myocardial infarction in this 79 year old man suggests that these procedures may have had a beneficial effect on the compensatory coronary circulation. This conclusion is in harmony with the known effects of somatic trigger mechanisms on visceral function (motorovisceral reflexes).

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CLINICAL PROGRESS

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The Patent Ductus Arteriosus

Observations from 412 Surgically Treated Cases

By ROBERT E. GROSS, M.D., AND LUTHER A. LONGINO, M.D.

A patent ductus arteriosus can be recognized with a high degree of accuracy by auscultation and simple office examination. Electrocardiographic and fluoroscopic studies are helpful, but it is rarely necessary to employ more elaborate and expensive forms of investigation. While the condition seldom causes serious incapacitation in early life, it is apt to be accompanied by a very high percentage of serious complications in later life. These facts give strong backing to the conviction that it is desirable to operate upon all children possessing a patent ductus—even though they are asymptomatic at the time—because it is technically much easier to perform a surgical closure of the vessel in this period. Ligation or suture-ligation is successful in a high proportion of cases, but a complete division of the vessel is the ideal method of therapy. In a consecutive series of 369 cases of division there have been no deaths from hemorrhage. The total mortality rate has been 2.1 per cent. For patients who had no complications prior to surgery, the mortality rate was under one-half of one per cent.

THERE have been many recent therapeutic advances in the fields of cardiology and surgery, among which is the fascinating chapter of cooperation between medical man and surgeon in the recognition of and the treatment of the patent ductus arteriosus and its various complications. During the past 11 or 12 years many articles have been written about various aspects of these problems, but no attempt will be made here to summarize in detail all of this material. Our purpose is merely to set forth for those interested in the subject a few comprehensive statements regarding the detection of the anomaly, the prognosis in untreated cases, the methods which are available for surgical correction, and the results of such operative procedures.

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THE CLINICAL PICTURE

When a ductus arteriosus remains open beyond the neonatal period, the individual has a shunt which is similar to an arteriovenous fistula. Such a communication may be tolerated extremely well if the possessor is fortunate enough to escape superimposed infection and if the shunt is a small one. Under such circumstances humans have had little or no incapacitation, and indeed have lived to advanced age. Unfortunately, such a favorable outcome is not encountered in a high percentage of cases; there are certain hazards which occur rather frequently: (1) The shunt may divert so much blood from the aorta that the peripheral circulation is robbed and the individual has a retarded physical development.

(2) The heart may increase its output, attempting to maintain the peripheral flow at a satisfactory level; while accomplishing this an exceedingly large amount of blood is passed back through the ductus. The individual may be well developed, and indeed be entirely normal in appearance, but the heart will come to embarrassment or failure. (3) Bacterial infection may be superimposed upon the vascular abnormality, the causative organism commonly being the *Streptococcus viridans*. In patients who have been followed over sufficiently long periods of time, the incidence of this complication is probably 25 per cent. (4) There are more rare complications such as aneurysmal dilatation or rupture. The first of the above-named complications appears in childhood, whereas the others are more apt to be problems of adult life, particularly of the third and fourth decades.

An excellent study of the prognosis for the adult with an untreated patent ductus arteriosus has been made by Keys and Shapiro.[6] They point out that subjects who are alive at 17 years of age with an open ductus have a life expectancy which averages only half that of the general population. While a patent ductus usually seems to be an innocuous affair when seen in children, long-term observations show that commonly the outlook is serious because of the likelihood of late incapacitation and shortening of life.

Individuals with a patent ductus arteriosus may have little or no evidence of cardiac embarrassment, or conversely, they may have marked invalidism, depending upon the age of the person and the size of the leak which exists. In general, the abnormality is tolerated well in childhood and decompensation is rare in that period. As a rule, youngsters have endless energy, can indulge in strenuous sports, and are thought to be entirely normal by their parents. In some instances, there is slight to moderate limitation of physical activity; extensive exercise is followed by dyspnea, palpitation, and excessive fatigue. Patients in midlife often have moderate cardiac embarrassment, less commonly they have all of the classical findings of failure. Adults frequently observe that they cannot maintain former levels of work, that fatigue is marked, or that long periods of rest are required. We are increasingly impressed by the number of individuals who present themselves in their thirties or forties, who have had no frank signs or symptoms of cardiac failure, but who have lost their pep and who drag about in their daily existence with no exuberance. While such people are by no means invalids in the common sense of the term, they are nevertheless incapacitated and are limited in their effectiveness and usefulness.

In an important percentage of cases, but by no means in the majority of them, the general physical development is somewhat retarded. When compared with normal children of the same age, the height and particularly the weight are distinctly less than the average normal; in some cases these findings are very striking. In no instance have we seen lack of mental development which could be rightfully ascribed to the presence of an open ductus.

Superimposed *Streptococcus viridans* infection is rarely found in childhood, though we have seen it as early as 4 years. The highest incidence of endocarditis or pulmonary endarteritis is in the third and fourth decades, following which time the frequency diminishes. The complaints include fever, persistent sweating, anorexia, weight loss, chest pain, and phenomena in various parts of the body suggesting arterial embolism. The latter almost certainly indicate that vegetations are not limited to the ductus region, but that they have also developed on the mitral or aortic valves. Blood cultures provide direct evidence of blood-stream infection, and they probably give some information regarding the severity of the invasion.

The physical findings in a case of uncomplicated patent ductus arteriosus are clear-cut. It is important to emphasize that simple examination (with stress upon an intelligent auscultation) can lead to a rapid and accurate recognition of this congenital abnormality in more than 95 per cent of the cases.

The color of the skin and the mucous membranes is normal in most instances, but some pallor is present in others. Cyanosis is never found, unless there is frank cardiac failure and a reversal of blood flow through the ductus. The nails are not clubbed. The heart is normal

or slightly increased in size; great enlargements are rare. The cardiac activity may be within normal limits, but if the ductus is large, there is an increased forcefulness of the impulse and there is a heaving pulsation over the neck vessels. These findings are more apparent in thin subjects than in heavy-set ones. By auscultation a very characteristic murmur is heard in the second or third intercostal space to the left of the sternum. It is continuous, is accentuated during systole, and dies off during diastole; it usually has a rumbling quality. The pulmonic sounds may be replaced by the murmur, or the second sound may be quite accentuated. The murmur has been well described as a "machinery" one, and the physician who has heard it several times should always be able to recognize it thereafter. It may be widely transmitted over the precordium, into the left axilla, up into the neck, or over the back particularly to the left of the spine. While all of the murmur might be transmitted, it is more common to have only the louder systolic portion carried to the cardiac apex, to the neck, or to the back. A ductus murmur is generally one of considerable intensity, and it is accompanied by a thrill in about one half of the cases. The thrill may be continuous or it may be limited to systole; it is most intense over the pulmonic region, and it is seldom felt far from this area.

On theoretic grounds—and from observations in a few patients—it is possible for a tiny ductus to produce a murmur which is limited to systole; under such circumstances the systolic murmur is always of very low intensity. In contrast, any moderate or loud systolic murmur (unaccompanied by a diastolic element) almost certainly arises from some other cardiac abnormality such as a septal defect or a pure pulmonary stenosis. Since 97 or 98 per cent of all ductuses have continuous murmurs, it is an excellent working rule to avoid making the diagnosis of a patent ductus arteriosus unless such a murmur is present.

It is well to bear in mind that the classical sounds of an open ductus may not be found if one is examining a patient (usually an adult) in failure. At that time the pulmonary artery pressure may be exceedingly high, so that a near-equalization between it and the aortic tension gives a reduced ductus flow, no flow at all, or even a reversal of flow. Such conditions will give, respectively, a murmur limited to systole, no murmur, or a variable murmur associated with intermittent cyanosis. A good description of such a case has been presented by Johnson and associates.[5]

Parents are often disturbed by the fact that a cardiovascular abnormality was not recognized by their physician in the first few years of life. It is important to restore confidence in their doctor by pointing out that it is often impossible to detect this anomaly in infancy. While it is true that some babies with a ductus have a continuous and easily detectable machinery murmur from birth, it is extremely common to find the following series of events. In the early months the aortic pressure is low and the pulmonary pressure is normally high; there is no appreciable flow through the ductus and there is no murmur. In the subsequent year or so the aortic pressure rises and the pulmonary pressure falls; there is some ductus flow which gives a systolic murmur. By the third year the aortic pressure is high and the pulmonary pressure is low; there is now a considerable ductus flow and a typical continuous murmur. From these facts it is obvious that the best of physicians might not have been able to hear an abnormality in early life. Furthermore, it is clear that if one hears a systolic murmur in the first year or two of life, it is not possible to exclude the presence of a ductus; under such circumstances it is well to examine the child again at 3 or 4 years of age, because if a continuous ductus murmur is ever to develop it will surely be present by that time.

While it is not necessary to discuss here all the important differential diagnoses, it is worthwhile to point out a small group of patients who have high interventricular septal defects which lie in such a position that the medial cusp of the aortic valve is incompletely supported, and hence collapses from time to time and gives aortic valve regurgitation. We have seen 10 such cases (about 1 to every 40 ductus patients). The murmur is most intense in the pulmonary area, but it does not have a

truly continuous quality. It is more properly described as a "to-and-fro" murmur, which on occasions is exceedingly difficult to differentiate from the continuous murmur of an open ductus. Patients with these high septal defects have a very low diastolic pressure (because of the aortic valve insufficiency), important A-V conduction defects by electrocardiographic tracings, and greatly increased pulsations of the aortic arch and pulmonary arteries by fluoroscopic study.

Ductus patients usually have systolic blood pressures which are normal for their respective ages. The diastolic level is normal or depressed, depending upon the size of the ductus. Small fistulas do not give any important change in the diastolic pressure, but large leaks are accompanied by diminutions to 50 or 40 mm. of mercury. When the pulse pressure is high, there may be a Duroziez's sign or a visible capillary pulsation in the nail beds.

The femoral pulsations are excellent, the blood pressures in the legs are above those in the arms—points of importance in ruling out a coarctation of the aorta.

In a rough way, it is possible to gain some impression of whether one is dealing with a ductus of small, medium, or large size. If the heart is normal in size or is only slightly enlarged, if the beat is not overly vigorous, if the x-ray changes are minimal, and if the diastolic pressure is only slightly diminished, it is reasonable to assume that the shunt is a relatively small one. On the contrary, if the heart is moderately enlarged, the murmur is intense and is possibly accompanied by a thrill, the diastolic pressure is moderately depressed, and the fluoroscopic findings are those of considerable left-right shunt, one can assume that the ductus is of moderate or average size. In rare cases (possibly 1 out of 40 or 50 patients) the heart is quite enlarged by physical examination, there is a heaving beat which shakes the patient's chest or even the bed on which he lies, there are forceful pulsations in the neck, there are marked fluoroscopic changes, and the diastolic pressure is markedly depressed (though in a few instances the pulmonary pressure may be so high that the peripheral diastolic pressure is not particularly low); one can instantly predict that the shunt is of tremendous size. Under these latter circumstances one is apt to hear additional murmurs which are indicative of a greatly augmented flow through the left side of the heart; the large amount of blood (which may be two or two and a half times normal) will set up murmurs as it rushes through a normal mitral or aortic valve orifice. Therefore, in addition to the continuous murmur in the pulmonary zone, one will hear a separate diastolic murmur in the mitral area, or a separate systolic murmur in the aortic region. It is important to recognize these occasional cases with tremendous shunts so that the patient's family can be informed of the risks which are much higher than those of average cases, and so the surgeon can be adequately prepared to deal with a situation which will present technical difficulties enormously greater than those which are ordinarily encountered.

Laboratory Findings

These patients do not have polycythemia.

Electrocardiographic tracings are helpful in a surprisingly small percentage of cases, and we have not depended upon them in more than 1 or 2 per cent of cases to help establish the diagnosis. In the vast majority of cases, particularly in children, electrocardiograms are normal and there is no axis deviation. In some tracings, particularly from adults, there may be left-axis shift, especially in the presence of a shunt of moderate or large size. Fibrillation or indications of myocardial damage may be found in some of the older subjects when the cardiac strain has been excessive. Electrocardiographic study is most valuable as a tool in excluding cases with other cardiac lesions. Particular attention should be given to the presence of any right-axis deviation, the finding of which should make one strongly suspect some other anomaly as a pulmonic stenosis or a tetralogy of Fallot. In only 4 patients have we found right preponderance when there was a pure patent ductus arteriosus; presumably the flow into the pulmonary circuit was very high and the right ventricle hypertrophied because it was pumping against an increased pressure. Whenever a prolonged P-R interval is encountered, one

should suspect that the auriculoventricular conduction apparatus is longer than normal and is probably stretched out around a septal defect.

Roentgenologic studies often help in the recognition of a patent ductus arteriosus, and film and fluoroscopic studies are also valuable in ruling out other cardiac abnormalities and rheumatic valvular disease. With a pure patent ductus the findings are indicative of a shunt from the aorta into the pulmonary circuit. The heart is slightly or moderately enlarged, particularly in transverse dimension; marked enlargement is rare. While it may be difficult to tell whether there is enlargement of one or both ventricles, not infrequently it is possible to show that the left chamber is the predominant one. Often the pulmonary artery (frequently incorrectly called the pulmonary conus) is fuller than normal and projects outward from the left border of the cardiac shadow. Likewise, vessels within the lung fields, particularly in the hila, are apt to have increased fullness. In about half of the cases the hilar vessels have a "hilar dance"; this may be quite difficult to observe, and too much reliance should not be placed upon the presence or absence of this point. Left anterior oblique and lateral views give evidence of left auricular enlargement in about half of the cases; this dilatation is best seen as an encroachment on the barium-filled esophagus. Such enlargement is dependent upon an increased flow through the left side of the heart; the left ventricle enlarges somewhat, whereas the thin-walled auricle dilates to a greater degree. Fluoroscopic observation and kymographic tracings generally show an augmented pulsation, particularly of the left ventricle, the aortic knob and the pulmonary artery. It is important to emphasize that roentgenologic findings are not specific for a patent ductus arteriosus; they may be mimicked by certain other lesions. A pure pulmonary stenosis is often accompanied by a considerable dilatation of the pulmonary artery beyond the obstruction. Septal openings are left-right shunts which give findings of an increased pulmonary flow. A fenestra between the first portions of the aorta and pulmonary artery gives roentgenologic pictures exactly like those of an open ductus. When the roentgenologist finds evidence of a left-right shunt, he is presented with the possibility of making several diagnoses. If in addition to an augmented pulmonary flow there is right ventricular enlargement, he should lean toward a diagnosis of interventricular septal defect. If there is associated right auricular enlargement, an interauricular septal defect is suggested. If there is no enlargement of the right side of the heart, he can be reasonably sure that the patient has a patent ductus (or one of the rare fenestras between the first portions of the aorta and pulmonary artery). If a ductus is small, the roentgenologic picture is normal or shows little change therefrom. Conversely, when the ductus is of moderate or large size, the roentgenologic findings are clear-cut and striking.

Cardiac catheterization can give direct measurement of various blood flows, and can give a reasonably accurate idea of the size of the shunt, but it is not necessary as a routine study for average cases. Of course, there are many patients with obscure abnormalities of the heart who should be studied by all means available, including catheterization, but it has been our experience that it is extremely rare to pick from this group a ductus which can come to operation which could not have been recognized by simpler means of roentgenography and cardiac auscultation.

More than 95 per cent of patent ductuses can be recognized with great facility and rapidity. While electrocardiographic studies and roentgenologic observations are helpful, it is well to emphasize that the vast majority of these lesions can be accurately detected in a few moments by intelligent use of the stethoscope. Furthermore, if a characteristic murmur does not exist in a given patient, too much stress should not be laid on laboratory or roentgenologic findings which might suggest the presence of a ductus, because operation under such circumstances will almost certainly lead to the finding of some other cardiovascular defect.

Considerations of Surgical Technic

It is not the purpose of this communication to discuss the details of operative technic; hence, only a few general statements will be made in this regard.

While we formerly employed cyclopropane

anesthesia for these cases, the fact that about half of our fatalities seemed to have been attributable to cardiac arrest or irregularity under this anesthetic has now influenced us to abandon cyclopropane and to employ ether and oxygen as a routine choice. Obviously, the anesthesia must be given with a closed system. An intralaryngeal tube should always be used to ensure an adequate airway at all times and to facilitate the suction-removal of any secretions from the lower respiratory tract. This gives the best chance for maintaining a quiet anesthesia during operation and it tremendously reduces the incidence of postoperative pulmonary complications.

There are some who have advised a posterior thoracic approach, an exposure which seems to us to be unduly complicated and quite unnecessary for the average ductus case. It is a more time-consuming exposure and closure. It certainly does not give the best view of the ductus. Its only possible superiority would be in the rare case with a huge ductus wherein one might want to place a large Potts-Smith-Gibson or a Freeman clamp on the aorta to isolate the ductus area without completely occluding the entire aortic lumen; such an application is impossible or is awkward from the antero-lateral approach. In all of our cases the chest opening has been through a left antero-lateral incision, made below the breast for cosmetic reasons, cutting the third intercostal muscles all the way around to the angle of the ribs. When handling adults, or when dealing with patients with large ductuses in whom maximum exposure is desirable, the cutaneous and latissimus dorsi incisions should be carried well around to the posterior axillary line. These exposures have been so satisfactory that we see little reason for changing them.

When the mediastinum is entered in front of the lung root, it is hardly necessary to emphasize that a thorough knowledge of the local anatomy, and of the congenital abnormalities which are apt to be encountered in this region, is a sine qua non. In so crowded a space a single false step can lead to disaster. Probably the biggest cause of failure in this type of surgery has been the trepidity of those who felt unsure of the exact positions of the large vessels; being fearful of setting up a rousing hemorrhage, they do not adequately free the ductus from its surrounding vestments. Under such circumstances it is almost impossible to tackle the ductus with any assurance of completing a thorough job. Conversely, an accurate anatomic knowledge of the area will allow one to proceed rapidly and without risk, to free the ductus entirely of all its coats, to clean off the adjacent aorta, and to mobilize adequately the nearby pulmonary artery. Only by such an extensive and thorough freeing can one subsequently deal with the ductus in a proper manner.

In the earlier part of our work only ligation of the ductus was employed, using various types of material to accomplish this. In a series of 43 cases it was found that 80 per cent of the patients obtained a complete obliteration and a permanent closure of the shunt, 10 per cent had the ligatures cut through and some of the fistula re-established, and the remaining 10 per cent had ligatures which were not put on tightly enough to close the vessel completely. While these over-all results might be considered satisfactory, it is obvious that they were not perfect. These observations are similar to those of Shapiro and Johnson[9] who analyzed (by personal communications with various physicians) 626 patients operated upon by 46 surgeons; the mortality rate in uninfected cases was 4.9 per cent and the incidence of recanalization was at least 8.7 per cent. Blalock[1] has developed a method of "suture-ligation" which is distinctly better than all of the ligation technics which we originally employed; it uses two encircling stitches at either end of the ductus, mattress sutures through the ductus, and an encircling tape of linen. Scott[8] has recently published a series of 161 closures of this type with excellent results. However, it has been widely recognized by vascular surgeons for many decades that closure of any large artery or shunt is most satisfactory when accomplished by a complete severance of the vessel; we believe that this fundamental principle also applies to the treatment of an open ductus for it gives the best assurance that the shunt has been completely closed off and that it will not recur. Complete division certainly seems to be the ideal method of therapy, provided it can be accomplished without assuming a high risk. While complete division

would seem to be fraught with dangers of uncontrollable bleeding, we have now performed 369 complete divisions without the loss of a single patient from hemorrhage at the time of operation or subsequent thereto. Eight of these ductuses were divided in patients who were being operated upon primarily for excision of a coarctation of the aorta. Obviously, the division technic requires more experience and care, yet we have found it possible to turn over a large number of these cases to assistant residents on the thoracic service who have performed a division in every instance without the loss of a single patient from hemorrhage. During the period in which we have divided the ductus in 369 cases, 3 patients have been encountered who had enormous shunts (larger than 1.5 cm. in diameter) from which we withdrew without any attempt to close the vessel; division seemed to be too formidable and risky; certainly any form of ligation or suture-ligation would have been ineffective and possibly fatal because of subsequent erosion and hemorrhage. With these rare shunts of great size some special technic must be developed, such as that suggested by Freeman and more recently by Conklin and Watkins.[2]

The patient's postoperative course can be made much more comfortable by injection of a local anesthetic in the posterior portions of the upper four or five intercostal nerves while the chest is open. For the last 10 years we have routinely infiltrated Nupercaine (in oil) in or about these structures, producing a regional hypesthesia which lasts for a week or 10 days.

A very careful closure of the chest has much to do with the patient's postoperative comfort and with the minimizing of accumulating fluid within the pleural cavity. In all cases some fluid does collect in the pleural sac, but in only a small percentage of subjects is this of sufficient degree to require postoperative tapping.

While chemotherapy is wholly unnecessary in many cases, there is some justification for using it as a routine prophylactic measure in the hope of avoiding postoperative pulmonary complications. It has long been our custom to give appropriate chemotherapy for 24 hours before operation and to continue it for four or five days thereafter.

Oxygen tents are not necessary during the postoperative period. If the left lung is kept in a state of full or nearly-complete expansion, the respiratory apparatus is functionally satisfactory and an oxygen tent is a needless encumbrance.

Patients can be allowed out of bed on the fourth or fifth day and can be ambulatory shortly after that. Routinely, they are discharged from the hospital on the eighth or ninth postoperative day. They are allowed increasing physical activity for the subsequent week or two, and ordinarily are back to complete and unrestricted activity or employment one month after operation.

Selection of Cases for Operation

From an intense interest for 12 years in the surgical therapy of ductus cases, the following general policies have been developed and adopted:

Certainly, there can be no disagreement with the recommendation that operation be undertaken for all patients with retarded physical development which cannot be accounted for on some other basis. Likewise, it is generally agreed that cardiac fatigue or failure demands operative closure of the shunt, so that the mechanical burden on the heart can be immediately reduced. Operation is also desirable for those subjects—mostly in the third and fourth decades—who do not show ordinary signs of cardiac failure but who nevertheless drag about with fatigue, a reduced activity, and a definite knowledge that it is becoming increasingly difficult to carry on the job of life. Such patients are more numerous than are those with classical findings of cardiac failure; to operate upon them is extremely satisfying, because they can be restored to normal life and vigor.

Regarding the possible benefits of surgery for patients who have blood stream infection with *Streptococcus viridans*, thinking has taken several turns during the past 10 years. During 1938 and 1939 when this serious malady could not be cured in more than 5 or 10 per cent of cases with the sulfonamides and other measures which were available, there seemed to be little theoretic reason why surgical closure of a shunt should be of much benefit. However, in

1940 Touroff and Vesell[10] showed in a dramatic way that such infection could be cured by obliteration of the ductus unaccompanied by sulfonamide therapy. In more extended observations, Touroff demonstrated that the cure rate could be raised to about 75 per cent by surgical means. We corroborated this with 9 recoveries in 12 infected cases which were surgically treated in the pre-penicillin era. By the mid-forties such recovery rates could be obtained, or even bettered, by penicillin therapy alone. This might seem to indicate that the infected patient should now be treated solely by penicillin, aureomycin, chloromycetin or one of the newer chemotherapeutic agents, but two additional factors should be taken into account. First, it must be borne in mind that subsequent attacks are not uncommon and it is possible that a second infection might come from an organism which is resistant to therapy. Second, while it is possible to cure infections in a high percentage of cases by appropriate chemotherapy, this does not necessarily mean that the entire cardiac mechanism can be returned to normal. There are many studies of patients whose infection has been dispelled but who in an appreciable percentage of cases are left as cardiac invalids because of the damage or scarring which remains in the myocardium. Obviously, the degree of such injury to the cardiac musculature depends upon such considerations as the duration and severity of the infection; it is known to vary greatly from case to case. The possibility that such pathologic change can reside in the musculature makes it desirable to reduce the mechanical load of the heart by surgically closing the open ductus. It is our present-day opinion that (1) Infected patients should be intensively treated by chemotherapeutic means for an appropriate length of time. If the blood stream cannot be sterilized by this alone, operation should be added during the active stage. (2) If it is possible to sterilize the blood stream by drugs alone—which can be accomplished in four-fifths of the cases—operation can be deferred for several months. This delay in operation has several advantages. In some cases it allows inflammatory reactions in the ductus wall to subside and thus lessens the technical difficulties of surgery. It allows the patient to recoup somewhat from the financial onslaught of an attenuated illness. It permits him to get out of the hospital for a period and to convalesce satisfactorily before undertaking a major operation. In summary, all infected cases should be treated by drug therapy plus surgery, the latter being either early or delayed, depending upon the efficacy of the drug therapy.

After a consideration of the above three categories (the physically retarded youngster, the patient with cardiac failure or fatigue, and the subject with superimposed infection) one is left with a large number of patients—particularly in the childhood ages—who have no important symptomatology and who repeatedly raise the question of whether or not operation should be advised. The answer to this query depends almost entirely upon the fatality rates and the promise of a permanent ductus closure which can be offered by the surgeon. Obviously, if surgical complications or mortality rates are high in a given institution, it is preferable to leave these young subjects alone. Conversely, in a large series of such patients we have been able to demonstrate that permanent closure can be assured by division of the ductus, that complications are almost nil, and that fatalities are distinctly less than 0.5 per cent. With this record, we feel fully justified in advising surgical closure of the ductus for all children and young adults, even though they are symptom-free at the moment. Without doubt, this approach will mean the subjection to operation of an occasional individual who admittedly might be fortunate enough to go through a long life with no important troubles from a small, open ductus. However, when considering the group as a whole, there can be no question about the fact that many future complications (such as cardiac fatigue and endarteritis) can be prevented and that the surgical risks are far less than is the risk of leaving such subjects untreated. Some clinicians still feel that it is preferable to avoid surgery for all who are asymptomatic, employing it only with those who develop complications in future years. This attitude certainly increases the surgeon's difficulties. Ductus operations in the young can be performed with relative facility, whereas

those in older individuals give much anxiety because the approach into the mediastinum is deeper, the regional vessels are more rigid and difficult to deal with, and the cardiac reserve is reduced. We are strongly impressed by the number of patients who had been entirely asymptomatic in childhood and in their teens, but who then present themselves in their twenties or thirties with symptoms which physicians would universally agree call for operative intervention. Operations on these older people do not carry higher fatality rates in our series but they certainly can tax the surgeon's ingenuity. A few experiences of this kind certainly indicate that it is far wiser and easier to operate upon patients in earlier years of life when the operative exposure is shorter, the cardiac reserve is greater, and the regional vessels are softer, elastic, and much easier to work upon. In summary, we believe that it is good "prophylaxis," which can be obtained at a negligible mortality rate, to advise surgical closure of the ductus for all children and young adults even though they are symptom-free.

Finally, what advice should be given those rather rare patients one sees in the middle years (35 to 50) or more advanced ages (above 50) who have always been symptom-free. These almost always have moderate-sized or small shunts, the larger ductuses having proved fatal in earlier life; the mechanical burden on the heart is therefore seldom excessive. Furthermore, these people, while not entirely free from the possibility of superimposed bacterial infection, have passed the years of peak incidence of this complication; it is becoming a decreasing menace for them. These considerations, plus the fact that operation in this time of life is certainly not easy, probably make it wise to avoid operation in the middle-aged asymptomatic group and to refuse it entirely in the older group. (This attitude for the asymptomatic middle-aged and elderly subjects should in no way make one hesitate to proceed with operation for anyone who has important symptoms in advanced years. We have operated upon a woman of 51 with marked incapacitation who was tremendously benefited by surgery.)

A consideration of the indications for operation should include some comment regarding the ages during which it is preferable to undertake this form of surgery. In general, if there are pressing indications for operation such as the stunting of physical growth, cardiac embarrassment, or superimposed infection, therapy should be undertaken with complete disregard for the age or size of the patient. We have operated upon an 11 month old baby who weighed but 13 pounds and who had marked physical retardation and also had cardiac failure; at the other end of the scale a woman of 51 was operated upon because of marked pulmonary hypertension and incapacitation. Both of these patients had excellent recoveries. Regarding operation on asymptomatic subjects, operation can be performed within a wide span of years. While it is quite possible to do so, there is seldom need for undertaking such a measure before 3 or 4 years. The surgeon still has excellent vessels to work upon until 15 or 20 years of age, though this limit is by no means a sharp one. In short, for the elective cases, optimum ages run from 3 or 4 years up to 15 or 20 years; the best chances for a smooth and relatively easy surgical procedure are generally provided between the ages of 6 and 12.

The age distribution of 412 patients in our series of surgically treated cases was:

years	*patients*
0–5	101
5–10	146
10–15	67
15–20	32
20–25	28
25–30	22
30–35	7
35–51	9

While many elective thoracic procedures were once thought to be performed most safely during summer months, this limitation no longer exists. There need be no hesitation about conducting ductus operations at any time of the year. During the last nine years we have not recognized any case of postoperative pneumonia, a situation which is attributed to the routine use of antibiotics before and after surgery and to the maintenance of a dry airway during operation.

An associated interventricular or interauricular septal defect is not a contraindication to surgical closure of an open ductus. A ductus does not compensate for either of these anomalies; all three defects are left-right types of shunts. Obviously, operation on a patient with an open ductus and a septal defect will not restore the cardiovascular apparatus to normal, but at least the heart can be considerably improved by taking off some of its mechanical burden. We have operated upon 19 such patients, all of whom survived.

Similarly, rheumatic mitral stenosis is not a contraindication to operative closure of the ductus, provided there is no important rheumatic activity at the time that operation is undertaken. Indeed, an associated rheumatic mitral stenosis is a clear-cut indication for surgical closure of the ductus, because such therapy will reduce the amount of blood which has to flow through the left side of the heart and the narrowed valve. Obviously, under these circumstances the cardiovascular apparatus cannot be made normal, but it can certainly be improved. We have operated upon 4 such individuals, all of whom survived.

The combination of pulmonary stenosis plus a patent ductus is rare; it is not a contraindication to operation on the ductus. A ductus in no way compensates for the bottleneck at the pulmonic valve (this is in contrast to the compensatory effects of a ductus in cases with a tetralogy of Fallot). Operative closure of the ductus is a desirable procedure, even though it will not return the cardiovascular apparatus to normal. We have operated upon 2 children with this combination of abnormalities; both survived. If in future years the pulmonary stenosis is of sufficient degree to produce important symptoms, the pulmonary valve opening can be enlarged by the Brock technic.

A word of caution is necessary regarding individuals who have any cyanosis, and who also have the auscultatory sounds of a patent ductus arteriosus. With these findings, the ductus should never be closed surgically, because it almost certainly is acting as a compensatory mechanism for a complicated cardiovascular defect.

Results of Surgical Therapy

The surgical treatment of a patent ductus arteriosus, while extremely promising since the earliest attempts, has been attended by falling fatality rates and by more satisfactory results. In the present day, these surgical undertakings should seldom be followed by any serious complications and the mortalities should not be more than a few per cent. In our series at the Children's Hospital and the Peter Bent Brigham Hospital of Boston 412 patients have been operated upon, 43 of whom had some form of ligation and subsequently 369 had complete division. In the latter group there have been 8 fatalities, giving an over-all mortality rate of 2.1 per cent. This series included a considerable number of patients who had some degree of cardiac failure and also 12 who had active infection at the time of operation. In those patients who were asymptomatic prior to operation, the mortality rate has been slightly less than 0.5 per cent. The cause of fatality in our division cases were as follows:

Case	*Age*	*Cause of Fatality*
1	15	Mediastinitis and bacteremia (*S. aureus*).
2	27	Cardiac dilatation, because of hypoplastic descending aorta.
3	3	Cardiac arrest from cyclopropane anesthesia.
4	4	Collapse immediately following operation, from cyclopropane anesthesia.
5	5	Cardiac arrest after ductus division. Cyclopropane anesthesia. Cerebral anoxia; death 48 hours later.
6	2	Cardiac arrest. ? cyclopropane death.
7	3	Cardiac arrest during mediastinal dissection, probably cyclopropane death.
8	11	Mediastinitis and bacteremia (*S. aureus*).

In the surviving patients certain changes have been found which will be separately considered as follows:

The diastolic blood pressure rises immediately to normal, the extent of rise varying with the depression which had existed prior to operation. When the leak from the aortic arch has been stopped, the peripheral system is able to maintain the diastolic pressure at normal physiologic levels.

In almost 90 per cent of the cases all murmur has disappeared following division of the ductus. In the remaining patients, the continuous machinery murmur has disappeared but there remains a systolic murmur which is believed to arise from a second cardiovascular defect or is a functional sound. Twenty-eight of these have as residual defects the following:

Septal defects	19
Pure pulmonic stenosis	2
Rheumatic mitral stenosis	4
Bicuspid aortic valve	3

In addition to these 28 with known pathologic lesions, there are a similar number who are left, following surgery, with a grade 1 or 2 soft systolic murmur in the pulmonic area which is not accompanied by any other physical sign, roentgenologic change, or electrocardiographic abnormality; we believe these murmurs to be functional, but it is of course possible that some of these patients do have minor intracardiac anomalies.

The activity of a heart strikingly diminishes after surgical closure of a ductus. This can be appreciated by inspection of the thorax, by noting reduced prominence in pulsations of the neck vessels, and by fluoroscopic or kymographic studies. A heart which before operation had a very heaving, pounding and forceful beat, will be found to have a postoperative activity which in comparison is quiet and much less vigorous. Postoperative diminution in cardiac action is not great if the ductus had been a small one; in contrast, obliteration of a large ductus is followed by a decrease in forcefulness which is quite evident to both physician and patient.

Some change in the over-all size of the heart can often be expected following closure of a shunt. Cardiac enlargement can represent hypertrophy or dilatation, but generally it is a combination of the two. If enlargement is due primarily to dilatation, this will disappear immediately following surgical closure of the ductus. If hypertrophy has existed, the heart apparently has little ability to shrink, but observations in a growing individual will show that the thorax and other body measurements increase during the subsequent year or two, whereas the heart grows very little during this period, at the end of which time a normal cardiothoracic ratio becomes established. When a ductus shunt has been small, there is little diminution in the size of the heart following operation; in contrast, when a fistula of large size has been closed, the over-all dimensions of the heart will decrease markedly. We have seen diminutions in transverse diameters of as much as 1.5 cm.

Individuals who had essentially normal physical development before operation show no important changes following surgery. However, underweight subjects, most of whom are in the childhood group, will exhibit a surprising and gratifying gain in weight to an amazing degree during the year or two subsequent to surgery. Apparently, closure of a shunt increases the peripheral flow of blood to the body and thereby improves the general physical state.

Eppinger, Burwell and Gross[3] and others have accumulated data on the changes in circulation following closure of a patent ductus arteriosus. The figures all clearly indicate that obliteration of the shunt can greatly diminish the output of the left side of the heart and presumably the cardiac reserve is accordingly improved.

In the pre-penicillin era 12 patients were operated upon during infection with *Streptococcus viridans*. Nine of these survived and were cured, whereas the others went on and eventually died of their infectious disease. Now that penicillin and other chemotherapeutic agents are available, one is not justified in using surgical means alone. We have employed surgery in 6 patients who had been already cured of their infection by penicillin or other drugs. All 6 of these have survived, and while it is not possible to make any objective measurements of gains which might have accrued, it is reasonable to believe that the closure of the shunt was of value in the rehabilitation of these subjects.

For those children and young adults who have been operated upon for "preventive" reasons there is universal agreement that they or their families feel better on psychologic grounds for having had the anomaly corrected. Many of these people had previously

harbored a fear that something disastrous was hanging over their heads, and they were much relieved when this anxiety was removed—a consideration of no small significance. While no objective measurements can be made of what has been accomplished, it is quite reasonable to believe that some of these individuals have been kept free of complications which might otherwise have developed. The majority of patients in our series have been operated upon for prophylactic reasons; they have been followed as long as 12 years, and none has yet developed endarteritis.

Summary

A patent ductus may exist through a long life with few if any symptoms, provided the leak is a small one. Commonly, patients develop cardiac fatigue in adult life, even though they might have been symptom-free in childhood and adolescence. Cardiac strain may be severe enough to lead to failure in adult life. If patients are followed for sufficiently long periods of time, superimposed infections will be found in about one-fourth of them. Patients with a ductus who reach maturity have a life expectancy which is only about half of that of the population as a whole.

Patent ductuses can be recognized with a high degree of accuracy by simple office examinations which are available to any physician. Fluoroscopic and electrocardiographic studies are helpful in the study of any patient with a cardiovascular anomaly, but a diagnosis of a patent ductus should rarely be made from these two tests if the patient does not have a typical continuous murmur in the pulmonary area. Angiocardiographic and catheterization studies are helpful in study of occasional patients, but they are not necessary for the recognition of average ductus cases.

Surgical treatment for the patent ductus arteriosus has now been carried out by many surgeons and clinics. The operation has been placed on a sound basis with over-all excellent results and with exceedingly low mortality rates.

It is clear that surgical closure of a ductus should be performed for those children with physical retardation in growth, for all who have any evidence of cardiac fatigue, embarrassment or failure, and for those who have bloodstream infection, even though the latter has been cured by chemotherapeutic means. Some clinicians prefer to defer operation for children and adolescent individuals who are symptom-free. It is our firm conviction, based on low surgical fatality rates, that it is advisable to operate upon all children and young adults who have an open ductus, believing that this prophylactic procedure is of considerable value in warding off cardiovascular complications in later years.

An open ductus can be closed by some form of ligation, by the improved suture-ligation technic of Blalock, or by complete division. We believe that the latter is the ideal measure and that it can be carried out satisfactorily as a routine procedure without undue risk, provided the operator is willing to study and develop the technic and has a reasonable familiarity with vascular problems. In a series of 412 ductus patients treated by operation the last 369 have had complete division of the ductus, without fatality from hemorrhage at the time of operation or subsequent thereto. In this division group there have been 8 deaths from various causes, giving an over-all mortality rate of 2.1 per cent. For patients who had no complications prior to surgery, the mortality rate was under 0.5 per cent.

Studies on patients who have been operated upon leave no doubt about the benefits of closure of a shunt of this type. Experience from many sources clearly indicates the effectiveness of surgical treatment when various complications have already developed. Follow-ups, some as long as 12 years, also give ample backing to the use of the operation as a prophylactic measure for patients who have not previously had cardiovascular symptoms.

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Franz Volhard
1872–1950

Professor Franz Volhard, who died on May 24, 1950, at the age of 78, can be considered not only as one of the most outstanding creative personalities in twentieth century German medicine but also as an example of moral strength during the dark years of the dictatorship which deprived him of his teaching position, and as an unbroken force, contributing courageously to the slow and painful rebirth of German medical science amidst the ruins of his shattered country. From 1918 until 1927 he was head of the Medical University Clinic in Halle; from 1927 until 1938 and again from 1945 until 1950, in Frankfurt.

Although Volhard's international fame is due mainly to his work in the field of renal and hypertensive disease, he was a clinician and investigator of considerable versatility, having contributed fundamental studies concerning the digestive enzymes, cardiac arrhythmias, valvular lesions, and many other matters of importance. His dilution and concentration tests of kidney function have become universal clinical standard procedures. His "hunger and thirst" treatment of acute glomerulonephritis still retains some of its merits and his perennial insistence on sodium restriction in the diet of hypertensive patients has paved the way for the modern concepts of the role of sodium in hypertension. Volhard's distinction between a "pale" and a "red" type of hypertension was originally based on plain visual observation but rational integration with clinical experience led to the postulate of renal and nonrenal forms of high blood pressure, the validity of which has been amply confirmed on both sides of the Atlantic.

By training and inclination Volhard was primarily a clinician but he gathered around himself a group of able younger investigators whom his enthusiasm inspired to important activities. Hülse and Bohn made the first groping steps in the search for a vasopressor substance in the body fluids of hypertensive individuals, Becher studied the toxic significance of phenols in the uremic blood, Sarre did pioneer work concerning the effect of desoxycorticosterone on the human blood pressure in relation to sodium metabolism. One of the most far-reaching experimental contributions which emerged from the Volhard school was Hartwich's production of hypertension through artificial partial kidney ischemia and it is characteristic of Volhard's mentality that he viewed Goldblatt's spectacular successes as well as other American achievements with satisfaction and admiration rather than with envy. Old age was no burden on his ever-searching mind. Only recently he became passionately interested in the hypothesis that an imbalance between the neural depressor and pressor tonus, elicited by a loss of distensibility of the aging carotid sinus area, might be involved in the mechanism of certain types of neurogenic hypertension. His countless publications were climaxed by a huge monograph on kidney diseases, known throughout Europe as the "kidney Bible."

He was a brilliant teacher and beloved by his students both for his didactic abilities and for his keen sense of humor and patriarchal benevolence. Honors of all kinds were showered on him; the Paris Sorbonne bestowed on him an honorary degree, but the Goethe medal, the highest German distinction for intellectual achievement, was denied him through the intervention of the National Socialist government.

Volhard was the father of ten children and being an excellent violinist he maintained in his home a distinctly artistic and highly cultured atmosphere. All in all he was a man who represented the vanishing pre-Hitler generation of German medical scientists at its very best.

W. Raab, M.D.

ABSTRACTS

BACTERIAL ENDOCARDITIS

Tang, W.: Studies of the Effect of Penicillin Treatment of Subacute Bacterial Endocarditis upon the Bacteria of the Valves of the Heart. Ztschr. f. d. ges. Inn. Med. **5:** 230 (April), 1950.

The author studied 12 cases of subacute bacterial endocarditis with respect to the presence of bacteria in the heart valves. Two cases died before treatment, 10 during or shortly following treatment, and 2 during reactivation after "successful" therapy. The total amount of penicillin used was between 4.4 and 32.5 million units. Bacteria could be demonstrated histologically in the valves in all cases. Cultures of the valves revealed growth of bacteria in the 2 untreated cases and in 1 of those subjected to treatment. The author concludes that antibiotics have an effect not only on the bacteremia, but also on bacteria within the valves.

PICK

Germer, W. D., Fischer, L., and v. Oldershausen, H. F.: Subacute Bacterial Endocarditis and Protein Lability tests. Ztschr. f. d. ges. Inn. Med. **5:** 219 (April), 1950.

In 50 cases of subacute bacterial endocarditis, serial determinations of the following values were performed: total protein, sedimentation rate, thymol turbidity and flocculation test, Takata-Ara reaction, Weltmann's reaction, cadmium reaction, formol gel reaction, citochol, Meincke and Kahn test, and xanthoprotein reaction.

The total proteins were normal in most of the cases. The sedimentation rate and the so-called protein lability tests (thymol, Takata-Ara, and Weltmann) were abnormal in all cases during activity. The rest of the tests had inconstant results. No correlation could be established between positive tests and the presence of reticuloendothelial elements in peripheral blood, spleen and liver, or liver damage. Protein lability tests (especially the simple thymol test) may be used as control reactions during treatment and are of value in the differential diagnosis of subacute bacterial endocarditis.

PICK

Ball, K.: Abacterial Form of Endocarditis with Necrosis of the Ears. Brit. M. J. 4664· 1236, (May), 1950.

The author presents a case of abacterial endocarditis in which the lesions consisted of a bicuspid aortic valve with yellowish red vegetations and narrowing of the anterior descending branch of the left coronary with healed infarct, in association with symmetrical necrosis of the helix of both ears. Unlike an embolic process, the course was slow in developing and remitting. Although myocardial infarction is a rarity in this condition, it was proved by electrocardiographic changes three months before death. Other atypical features consisted of progressive renal failure, repeated sterile cultures, signs of liver damage, proved by liver function tests, and failure of the patient to respond to penicillin. The author suggests that a heightened immunity of the host accounted for the absence of bacteremia and possibly for the visceral lesions as well. He feels that the abacterial form of endocarditis is a clinical entity.

TANDOWSKY

BLOOD COAGULATION

Henstell, H. H., and Henstell, I. S.: The Electrolytic Resistance of the Blood Clot in Thrombocytopenia and its Relationship to the Platelet Concentration. Am. J. Clin. Path. **20:** 362 (April), 1950.

Besides a marked reduction in the number of circulating platelets in thrombocytopenic purpura, the authors also found a greatly depressed electrolytic resistance of the whole blood clot. The alteration appeared to be related in large measure to the degree and strength of clot retraction, as measured by the percentage of volume of clot. Following splenectomy, there was a prompt rise in the clot resistance and platelet count and a prompt fall in percentage of volume of clot. However, there was a lack of correspondence between the level of the platelets and the clot resistance both in the untreated patients and following splenectomy. Because of such a finding, the question was raised as to whether platelets in different clinical conditions vary in their capacity to affect clot retraction or whether other factors influence this reaction.

ABRAMSON

Shinowara, G. Y., and Smith, W. B.: Enzyme Studies on Human Blood. VII. Prothrombin as Determined with the Isolation Technic, in Patients Receiving Dicumarol. Am. J. Clin. Path. **20:** 341 (April), 1950.

The effect of dicumarol on the prothrombin level of 10 patients was studied using the one stage technic of Quick and a new isolation procedure for the estimation of prothrombin. In the patients receiving an average of more than 80 mg. of dicumarol daily, the initial fall of prothrombin determined by the one stage method was found to be much more precipitous than that determined by the isolation technic. After a week of therapy the two prothrombin technics showed excellent correlation when the isolation level was below 30 per cent of normal. When it rose above 30 per cent, the one stage technic tended to show lower values. The prothrombin results with the isolation technic were not altered by heparin, whereas those obtained with the one stage technic showed a definite diminution for about four hours after injection of the drug.

ABRAMSON

Rose, W. McI.: Anticoagulants in the Management of Cerebral Infarction: A Record of the Poor Result Obtained. M. J. Australia **1:** 530 (April), 1950.

Twenty-four cases of cerebral infarction were studied. Twelve cases were seen within 24 hours after the onset of symptoms. Six of these received heparin and dicumarin and 6 received dicumarin only. In no case was dramatic improvement seen. In 6 cases seen between 24 and 48 hours after the onset, only dicumarin was given. Striking improvement occurred in 2 cases, (however, the prothrombin time had not reached therapeutic levels when this occurred) no effect was seen in the other 4 cases. The 6 patients treated with dicumarin between the second and seventh days after onset were not benefitted. Two patients of the series died of cerebral hemorrhage. Three patients who had "spasm" of cerebral arteries with minor cerebral disturbances were treated with dicumarin without benefit.

BERNSTEIN

Glass, G. B. J.: The Thermal Coagulation Point of Blood Serum. Am. J. Med. **8:** 745 (June), 1950.

The thermal coagulation point of serum is the minimal temperature which in one minute will coagulate blood serum so that the coagulum does not break when subjected to standard shaking. Normally this temperature is 75 to 80 C.; in patients with cancer, cardiac failure, pregnancy, nephrosis, and severe infections, it is higher. The test parallels neither the sedimentation rate nor the Weltmann reaction, but depends mainly upon the qualitative and quantitative changes in serum albumen.

The author presents the results of 1500 tests on 1160 patients with various diseases. Two-thirds of patients with congestive heart failure showed altered thermal coagulation. Highest values occurred in patients with peripheral edema or transudate in a serous cavity. Extensive frostbite and burns also gave altered thermal coagulation points. The test cannot be used to screen early cancer because of the large percentage of false results.

HARRIS

Cosgriff, S. W.: Prophylaxis of Recurrent embolism of Intracardiac Origin. J. A. M. A. **143:** 870 (July 8), 1950.

Eighteen patients, the majority of whom had rheumatic heart disease and auricular fibrillation, were studied because they had experienced one or more emboli from intracardiac sources. They were treated for as long as two years with continuous dicumarol therapy while ambulatory. While it is impossible to state that recurrent emoblism was significantly reduced by this treatment, the clinical course during and subsequent to therapy strongly suggests that a favorable effect was produced. The patients were hospitalized and stabilized with daily prothrombin determinations. On the average maintenance dose, (50 to 100 mg. daily) it was impossible to obtain satisfactory control by determining prothrombin time once every week. The prothrombin level was checked every two weeks in two patients, but the author feels that weekly checks are safer.

Continuous dicumarol therapy of ambulatory patients is feasible provided there is careful supervision and adequate laboratory control. This group of patients received dicumarol for a combined total of

more than 200 months without untoward complications.

KITCHELL

Schilling, F. J.: Anticoagulants in Myocardial Infarction. J. A. M. A. **143:** 785 (July), 1950.

The author reports a series of 120 cases of myocardial infarction, all treated by the same conventional methods, except that 60 patients received anticoagulants and the other 60 did not. The case fatality rate for the treated group was 16.7 per cent and for the untreated group 40 per cent. In the group of patients who did not receive anticoagulant therapy, 18.3 per cent died of associated thromboembolic complications. In the treated series, no one died from thromboembolic complications alone (3.3 per cent died from thromboembolic complications in association with other complications). The difference in mortality in the two groups is significant. Of the patients who developed thromboembolic complications eleven of the untreated group died whereas none of the treated group died of this complication alone. The incidence of thromboemoblic complications was 25 per cent in the control group compared to 5 per cent in the treated group; this is both clinically and statistically significant.

The author advises the use of heparin and dicumarol in all cases of myocardial infarction, provided no contraindications to the use of these substances exists. The author states the anticoagulant drug should be administered only be persons having access to reliable facilities for prothrombin determinations, in the case of dicumarol, and clotting time tests, in the case of heparin.

KITCHELL

CONGENITAL ANOMALIES

Thomson, J.: Congenital Heart Disease Associated with Subdiaphragmatic Lateral Heterotaxy. Brit. Heart J. **12:** 147 (April), 1950.

The author reports 2 instances of congenital heart disease associated with subdiaphragmatic lateral heterotaxy. He believes more instances would be discovered if routine roentgen films were made of the abdomen in congenital heart disease.

SOLOFF

Holling, H. E., and Zak, G. A.: Cardiac Catheterization in the Diagnosis of Congenital Heart Disease. Brit. Heart J. **12:** 153 (April), 1950.

The authors review their experience in catheterizing 70 patients with cardiac malformations. They state that the method is not without danger and therefore should be used only when the diagnosis is in doubt or to obtain information not otherwise obtainable. Six of the 70 catheterized patients developed pulmonary or systemic thrombosis.

The authors point out that considerable differences in oxygen content may occur in the superior vena cava, inferior vena cava, right atrium and right ventricle, so that at times values for the normal and for defects may overlap. In the absence of shunts, the oxygen content of the right atrial blood is no greater than 2 volumes per cent of that of the superior vena cava, 3 volumes per cent of that of the inferior vena cava and 2 volumes per cent of the mean of both venae cavae. The oxygen content of the right ventricular blood is no more than 1 volume per cent of that of the right atrial blood and may be as much as 0.5 volumes per cent less than that of the pulmonary artery.

SOLOFF

Mannheimer, E.: New Viewpoints Concerning the Diagnosis of Patent Ductus Arteriosus. Arch. d. mal. du coeur **43:** 324 (April), 1950.

The author describes 4 cases of patent ductus arteriosus in patients between 5 and 12 years of age. None of these had continuous murmurs, as proved by phonocardiography, but the second sound was followed by some diastolic vibrations. The hearts of all 4 patients were notably enlarged; x-rays revealed in each a large left ventricle and a prominent pulmonary knob. Catheterization of the right heart revealed high pressure in the pulmonary artery (55 to 85 mm. Hg., systolic; and 30 to 40 mm. Hg., diastolic). The author attributes the absence of a frank diastolic murmur to this pulmonary hypertension. Surgery corrected the congenital abnormality in all cases.

LUISADA

Kirklin, J. W., and Clagett, O. T.: Vascular "Rings" Producing Respiratory Obstruction in Infants. Proc. Staff Meet. Mayo Clin. **25:** 360 (June), 1950.

The authors feel that probably only a small percentage of the anomalies of the aortic arch are associated with symptoms of tracheal or esophageal obstruction. In such instances, the symptoms often begin shortly after birth. Wheezing, stridor, cough, episodes of choking and cyanosis predominate among the respiratory symptoms. Because of the pressure on the trachea, secretions are frequently retained and recurrent episodes of pneumonia may result. Symptoms of esophageal obstruction may or may not be present; in certain anomalies the esophageal symptoms far overshadow the respiratory ones. Dysphagia is most likely to become prominent at the time semi-solid and solid foods are added to the baby's diet.

The roentgenologic observation of the various defects produced by the pressure of the vascular structures on the barium-filled esophagus is the most important diagnostic step. On occasions, roentgenologic examination of the trachea, either with or without the introduction of iodized oil, is of value. Angiocardiography is seldom necessary.

It is advantageous to operate on these patients as early in life as possible in order that normal growth

and development may proceed. In addition, prolonged pressure on the trachea can lead to softening of the tracheal rings. If such softening has occurred, partial collapse of the trachea may continue after operation with persistence of some symptoms.

SIMON

Lindert, M. C. F., Correll, H. L.: Rupture of Pulmonary Aneurysm Accompanying Patent Ductus Arteriosus. J. A. M. A. **143:** 888 (July 8), 1950.

The authors describe a case with an extremely unusual combination of vascular lesions. The patient, a 67 year old white woman, had a patent ductus arteriosus and an aneurysm of the pulmonary artery. A dissecting aneurysm of the thoracic and abdominal aorta was also present. According to the authors, only 5 cases are reported in patients beyond the age of 65 years (two of these were associated with pulmonary aneurysm). The present case is the sixth one. Aneurysm of the pulmonary artery is somewhat rare, there being only 147 cases proved by necropsy in the literature. Twenty-nine of these cases were found in conjunction with patent ductus arteriosus and this case brings the total to 30. The dissecting aneurysm, which had produced symptoms of pain, was not the final cause of death. This was due to rupture of the left branch of the pulmonary artery where it joined the pulmonary aneurysmal sac.

KITCHELL

Evans, P. R.: Cardiac Anomalies in Mongolism. Brit. Heart J. **12:** 258 (July), 1950.

Forty-seven anomalies of the heart or great vessels were found in 28 of 63 mongols who were examined post mortem. Slightly over one third were atrial and ventricular septal defects, and one sixth were patent ductus arteriosus. Most of the remaining lesions were pulmonary stenoses. The most common anomaly was a defect of the pars membranacea of the ventricular septum. It appears that cardiac anomalies in mongolism are due predominantly to defects occurring in the earlier stages of cardiac development.

SOLOFF

Denolin, H., and Lequime, J.: Situs Inversus with Associated Cardiovascular Malformation. Observations on Two Patients. Acta Clin. Belg. **5:** 168, 1950.

Two cases of dextrocardia with situs inversus are reported in whom catheterization revealed a trilocular heart with a single auricle. One subject had, in addition, two superior venae cavae and pulmonary stenosis. Two similar cases have been reported, one by Taussig (1947) and one by Cournand and his group (1949).

HECHT

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Gertler, M. M., and Garn, S. M.: Lipid Interrelationship in Health and in Coronary Artery Disease. Science **112:** 14 (July), 1950.

The authors studied the interrelationship between serum cholesterol and phospholipids among 243 male subjects, 97 of whom had a myocardial infarction before age 40. The remainder served as controls. Significantly higher levels of serum cholesterol, phospholipids and cholesterol:phospholipid ratio were found in the coronary group. The normal age trend was masked in the coronary group, for the correlation between age and the two lipids was not significant. Because of other evidence that serum phospholipids may have a protective action in experimental atherosclerosis, the authors believe that one of the factors favoring the deposition of cholesterol in the intima is enhanced, because of a relative lack of colloid stabilizer which may be reflected by the smaller rise in serum phospholipids.

WAIFE

Somerville, W., and Levine, S. A.: Angina Pectori and Thyrotoxicosis. Brit. Heart J. **12:** 245 (July), 1950.

Twenty-four instances (18 men and 6 women) are reported of thyrotoxicosis associated with angina pectoris. In most instances, thyrotoxicosis had been overlooked. Thirteen of 15 patients subjected to subtotal thyroidectomy and 4 of 5 treated with thiouracil were improved. Of the cases studied, 2 had normal basal metabolisms, 15 had normal blood pressures, and all had heart rates above normal. Only 7 of 22 had normal electrocardiograms. Eleven of 23 showed x-ray evidence of cardiac enlargement.

The angina pectoris was characterized by (1) its occurrence at rest and frequently while in bed, (2) its recent onset, usually within several months before examination, and (3) its abrupt lessening in frequency and often abrupt cessation following the use of iodine or thiouracil as preoperative medication. The prognosis of angina of decubitus with thyrotoxicosis is better than that associated with coronary artery disease.

SOLOFF

Howell, D. A., and Turnbull, G. C.: Hypertension and Effort in Cardiac Rupture following Acute Myocardial Infarction. Quart. Bull., Northwestern Univ. M. School **24:** 100 (Summer), 1950.

In 8 of 111 patients who died following acute myocardial infarction and came to necropsy, the cause of death was cardiac rupture. In 7 of the 8 cases, the heart was hypertrophied. Also, in 7 of the 8 cases the blood pressure remained at hypertensive levels from the onset of the symptoms of myocardial infarction until the occurrence of rupture. In only 5 of the remaining 103 patients did the blood pressure remain at a hypertensive level following infarc-

tion. The height of the intraventricular pressure plays an important role in the pathogenesis of cardiac rupture following acute myocardial infarction. Patients who show sustained hypertension following acute myocardial infarction should be given the benefit of absolute bed rest, and extra precautionary measures should be taken to protect against undue effort.

GELFAND

CONGESTIVE HEART FAILURE

Rader, G. E., and Goodman, R. D.: Congestive Heart Failure in Utero. J. Pediat. **36:** 230 (Feb.), 1950.

A case report of a premature infant who showed both clinical and necropsy evidence of having had congestive heart failure in utero is presented. Clinically, at birth, there was moderate generalized edema and ascites, although the lungs were clear. Pathologic findings were consistent with the diagnosis of congestive heart failure, as indicated by the predominance of passive congestion in the abdominal viscera, extremities, and pericardium in contrast to the relative absence of congestion in the lungs. The chief cardiac finding was the presence of pulmonic stenosis. In general, one must consider congestive heart failure in addition to erythroblastosis fetalis, sclerema, scleredema, hypoproteinemia, sodium retention, and syphilis in the differential diagnosis when a newborn infant presents the clinical picture of generalized edema.

SCHWARTZ

Anderson, G. M., and Hull, E.: The Effect of Dicumarol upon the Mortality and Incidence of Thromboembolic Complications in Congestive Heart Failure. Am. Heart J. **39:** 697 (May), 1950.

The authors studied the effects of dicumarol as an adjunct to the therapy of 147 patients with congestive heart failure. A contemporary group of 150 patients served as controls. All of the patients had initial prothrombin values above 50 per cent of normal. The 2 groups were similar with respect to age, sex, race, and severity of failure. The mortality of the treated group was 7.5 per cent, and of the control group, 13.3 per cent. Thromboembolic complications occurred in 2 per cent of the treated patients and in 8 per cent of the controls. Thromboembolism was a major factor in the deaths of 9 subjects of the controls. Thromboembolism was a major factor in the deaths of 9 subjects of the control group. If these 9 deaths were excluded from the control group, the mortality rate of both groups would be the same, indicating the effectiveness of dicumarol in the prevention of intravascular thrombosis.

HELLERSTEIN

ELECTROCARDIOGRAPHY

Schenneten, F.: Clinical-Electrocardiographic Observations of Cardiovascular Disturbances in Epidemic Hepatitis. Ztschr. f. d. ges. inn. Med. **5:** 56 (Jan.), 1950.

The auther describes abnormal electrocardiograms occurring in the course of epidemic hepatitis. During the subacute stage one case showed in a single record a normal ST-T changing gradually to S-T segment depression and to T wave inversion in leads I and II. This change is ascribed by the author to the presence of neurocirculatory asthenia following the infection. S-T depression, flattening of T waves and prolongation of the Q-T distance were seen in 2 other cases with the development of hepatic coma and were, in the author's opinion, due to subendocardial echymoses, found in one case at autopsy. Five other cases showed a tendency to low voltage in the limb leads, which the author believes was due to a hydropericardium.

PICK

Gallavardin, L., Froment, R., and Balestrier, G.: Paradoxical Persistence of Retrograde Conduction in Complete A-V Block. Arch. d. mal. du coeur **43:** 114 (Feb.), 1950.

The authors present a case of complete auriculoventricular block with "retrograde auricular conduction." The patient was followed for an entire year but, in spite of certain spontaneous variations of the auricular rate and of several injections of atropine, the block persisted unchanged. Occasionally, auricular contractions occurred with a fixed R-P interval (0.13 to 0.14 seconds). Carotid sinus compression, by slowing the auricular rate, increased the frequency of "retrograde conduction." Atropine, by causing rapid auricular rate, led to its disappearance. The "retrograde" contraction of the auricles was marked by inverted P waves mostly falling between R and T. Both the mechanical theory and that of the retrograde conduction are presented by the authors, who accept the second explanation. The possibility that the bundle of His conducted stimuli only in a backward direction is, therefore, admitted. The authors stress the fact that retrograde conduction in cases with complete heart block is extremely rare.

LUISADA

Evans, E., and Black, T. C.: The Electrocardiogram in Pneumoperitoneum. Am. Rev. Tuberc. **61:** 335 (March), 1950.

Ten tuberculous patients with pneumoperitoneum, showing no evidence of heart disease, were studied with standard and augmented unipolar extremity electrocardiograms, unipolar chest leads and esophageal leads, and with anteroposterior and lateral roentgenograms. In all 10 patients roentgeno-

grams showed that the heart was displaced upward and forward. Displacement was to the right in 1 of 4 patients with left phrenemphraxis, and to the left in 3 patients with right phrenemphraxis and 1 of 3 patients with pneumoperitoneum without phrenemphraxis. In 3 of the 4 patients with left phrenemphraxis and 2 of the 3 patients with pneumoperitoneum only, no appreciable lateral displacement was noted.

It was found that pneumoperitoneum may result in abnormal Q waves in the standard or unipolar limb leads or the esophageal leads. In each of the 10 cases abnormally large Q waves, usually associated with abnormal T waves, were obtained in esophageal leads at ventricular levels. The position of the heart, especially forward displacement, rather than interposition of air between the electrode and the heart, appeared to be a factor in the production of the consistently abnormal esophageal Q waves. Assumption of the upright position generally caused an increase in the amplitude of the esophageal Q and R waves with a decrease in the Q/R ratio; the T waves decreased in amplitude or became more deeply inverted.

SCHWARTZ

Ruff, S., Fedtke, H., and Ammon, R.: The Effect of Cytochrome C on the Anoxemia Electrocardiogram in Man. Ztschr. f. Kreislaufforsch **39:** 146 (March), 1950.

Five healthy subjects between 21 and 38 years old with normal electrocardiograms were exposed to low oxygen tension in a low pressure chamber. At an oxygen pressure corresponding to an altitude of 6.5 kilometers (20,000 feet), changes in the electrocardiogram consisting of low voltage of P, QRS, and T were noted. These changes could be immediately and completely abolished by two succeeding intravenous injections of 44 mg. of cytochrome C. This observation supports the assumption of an enhancing effect of cytochrome upon tissue respiration.

PICK

Hagen, P., and Freeman, Z.: The Electrocardiogram in Old Age. M. J. Australia **1:** 499 (April), 1950.

The 56 males studied ranged from 65 to 93 years of age, the average being 78 years. By the use of the unipolar limb leads, heart position was determined. The authors found that among 31 horizontal hearts there were 25 examples of left axis deviation and 2 examples of left heart strain pattern. Four hearts showed no axis deviation. Of the 18 vertical hearts, 12 showed no axis deviation, 3 showed left axis deviation, 1 had a left heart strain pattern, and 2 showed right axis deviation. The 3 "intermediate" hearts showed no axis deviation. Abnormalities in the electrocardiogram were analyzed as follows: 4 cases of bundle branch block, all right-sided; 1 case of right ventricular hypertrophy; 2 cases of first degree heart block; 2 cases of ST-T depression in the precordial leads; 6 cases of flat or inverted T waves in the precordial leads. This very low incidence of flattening or inversion of the T waves in the electrocardiogram of the aged indicates that we must reconsider dismissing such a pattern as "physiologic" even if the subject is over 70 years of age. However, whether the finding of an abnormal T wave in this age group carries prognostic significance is something yet to be evaluated.

BERNSTEIN

Dunn, F. L., and Rahm, Jr., W. E.: Electrocardiography: Modern Trends in Instrumentation and Visual and Direct Recording Electrocardiography. Ann. Int. Med. **32:** 611 (April), 1950.

The authors state that many of the easily available potentialities of electronic devices have not been utilized in electrocardiography, and until very recently the trend has been to imitate the recordings of the string galvanometer. A comparison between clinical electrocardiographs and a direct coupled cathode ray electrocardiograph was made on 10 normal males. Restrictions of frequency response of the clinical electrocardiographs tested resulted in definite distortions of the electrocardiogram components and loss of fine detail. Modern developments in cathode ray tube and electronic devices permit the assembly of multichannel electrocardiographs of high fidelity at low cost both for visual observation and photographic recording. A cathode ray electrocardiograph is illustrated and its value discussed from the standpoint of fidelity, visual and photographic observations, and use in conjunction with a direct recording electrocardiograph for making electrocardiographic surveys.

WENDKOS

Goldberger, E.: An RS-T Pattern Associated with Myocardial Injury. Brit. Heart J., **12:** 141 (April), 1950.

The author describes an RS-T pattern characteristic of myocardial injury found in 13 of 160 instances of myocardial disease and not encountered once in 50 normal electrocardiograms. The pattern is characterized by the RS-T segment beginning above the base line, descending in a gentle slope, and then rising to merge with the peak of positive T wave. The lowermost part of the segment is equidistant from the beginning of the segment and the peak of the T wave.

SOLOFF

Wosika, P. H., Feldman, E., Chesrow, E. J., and Myers, G. B.: Unipolar Precordial and Limb Lead Electrocardiograms in the Aged. Geriatrics **5:** 131 (May-June), 1950.

Electrocardiograms, including standard limb

leads, Goldberger limb leads, and Wilson precordial V leads (minimum of 6) were obtained upon 100 patients 80 years of age or older (average 84.2 years). Twenty patients had normal electrocardiograms; 15 of these showed no clinical evidence of cardiovascular disease; 4 showed arteriosclerotic heart disease, and one had hypertensive cardiovascular disease. Thirty patients, considered normal on clinical grounds, had abnormal electrocardiograms.

The largest groups of electrocardiographic abnormalities were: left ventricular hypertrophy, 31 per cent; prolonged auriculoventricular conduction time, 29 per cent; myocardial infarction, 14 per cent; bundle branch block, 12 per cent. In many instances abnormalities were diagnosable from a study of multiple leads, but not from the three standard and a single precordial lead, particularly in cases of ventricular hypertrophy and myocardial infarction.

The higher incidence of significant abnormalities in this group than in previously reported series may have been due in part to the older age of the patients, but it was also attributable to the use of multiple precordial and unipolar limb leads.

GELFAND

Magidson, O., Barber, J. M., and Wood, P.: Atrial Septal Defect, with Special Reference to the Electrocardiogram, the Pulmonary Artery Pressure, and the Second Heart Sound. Brit. Heart J. **12:** 277 (July), 1950.

An analysis is made of 62 instances of atrial septal defect, 21 confirmed by cardiac catheterization. There were 43 females and 19 males, 53 per cent of whom were above the age of 30 years. All of the patients had a systolic murmur, which in 52 of them was maximal over the pulmonic artery. A diastolic murmur along the left border of the sternum was present in 36 cases. The second sound was accentuated in only 27 cases, and was widely split in 52. This phenomenon is attributed to right bundle branch block which was present in 95 per cent of the series. The P waves in most cases were within normal limits. The P-R interval was at the upper limits of normal, and in 11 patients exceeded 0.22 second. X-ray may show enlargement of the right ventricle and pulmonary plethora, but in children the x-ray may fall within normal limits. Pulmonary hypertension was absent. Blood samples from the right auricle, right ventricle, and pulmonary artery were between 80 and 90 per cent saturated, with a normal value (70 per cent) for samples from the venae cavae.

SOLOFF

Leatham, A.: The Chest Lead Electrocardiogram in Health. Brit. Heart J. **12:** 213 (July), 1950.

The author describes the normal pattern and variation of the electrocardiogram in the chest leads of 100 healthy adults with the indifferent electrode both on the right arm and at Wilson's central terminal. The CF leads were discarded after the first 50 studies because of their variability. The CR and V leads have a similar coefficient of variation for the R, S, and T waves in most leads. V leads show fewer S-T segment variations and a clearer division into right and left patterns. In general, the positive deflections of the CR leads tend to be greater than those of the V leads.

SOLOFF

Deglaude, L., and Laubry, P.: Remarks on the Technic and Interpretation of Esophageal Leads. Arch. d. mal. du Coeur **42:** 861 (Sept.), 1949.

The authors studied the potentials created by the heart above and below the diaphragm in normal persons and in patients with healed myocardial infarction. Tracings were made from two positions within the gastric cavity, the electrode being placed respectively over the antero-inferior and postero-inferior surface of the ventricles. Tracings were also made with the electrode in the esophagus approximately at the level of the A-V groove and over the center of the left auricle.

It was found that the normal pattern of the gastric leads is a qR complex and a positive T. The Q wave, which never exceeds 3 mm. in amplitude and 0.03 second in duration, is ascribed to the normal initial left-to-right septal activation. In vertical hearts a similar contour is found in aV_F but the pattern of these two leads differs in horizontal hearts. In the esophageal leads a deep Q and inverted T are found normally in both positions used by the authors; these are ascribed to the reflection of intracavity potentials. In healed myocardial infarction these leads may provide information on the extension of the infarcted area. An abnormally deep and broad Q wave is found in the anterior gastric position in infarcts involving the apex. A deep Q found in both gastric leads indicates an extensive necrosis of the diaphragmatic portion of the heart.

PICK

Segers, M.: The Cause of Tracings of Ventricular Preponderance. Acta cardiol. **5:** 288, 1950.

The author studied the problem of ventricular preponderance in cases where the picture of "preponderance" occurred intermittently and started suddenly, either after exertion or because of premature auricular contractions. The different signs of "preponderance" appeared at the same time in the limb leads. Flattening or inversion of T occurred frequently in the chest leads, corresponding to the "preponderant" ventricle.

The author excludes both a structural lesion and coronary ischemia because of the sudden appearance; he excludes "bundle branch block" because no delay of QRS was found in the chest leads. The only possibility seems to be that of a delay in transmission within the interventricular septum with unilateral

invasion of the latter (septal block). This differs from the common "bundle branch block" where the disturbance occurs, according to the author, within the ventricular wall (partial block). Septal block of one side may be associated with parietal block of either the same (common) or the opposite side (less common). Curves of the type $S_1S_2S_3$, Tn, are also due to association of septal with parietal block.

LUISADA

Myers, G. B.: The Form of the QRS Complex in the Normal Precordial Electrocardiogram and in Ventricular Hypertrophy. Am. Heart J. **39:** 637, (May) 1950.

The author presents a series of diagrams which reconstruct the portion of the QRS complex registered in the 6 Wilson precordial leads at fixed intervals after the onset of the initial deflection. This method of analysis is offered to simplify for the beginner the concepts of Wilson and associates. The characteristic features of the QRS complex in the normal precordial electrocardiogram, in left ventricular hypertrophy, and in right ventricular hypertrophy are presented.

HELLERSTEIN

ENDOCRINE EFFECTS ON CIRCULATION

Goldzieher, M. A.: The Role of the Adrenal Glands in the Utilization of Oxygen. J. Aviation Med. **21:** 153 (April), 1950.

Air hunger is a conspicuous symptom in the adrenalectomized animal and in cases of destruction of the adrenals in the newborn. The physiologic hypertrophy of the fetal adrenal cortex is a phenomenon due to low oxygen saturation and tension of the fetal blood. The physiologic involution of the cortex after birth expresses the decreased need for cortical hormone upon onset of pulmonary respiration. There is absence of involution in the "blue baby." Tissues from adrenalectomized animals lack the ability to use oxygen but regain it when cortical extract is given. Oxygen consumption cannot be stimulated by the thyroid hormone without the aid of the cortical hormone. Adaptation to long exposure to oxygen deficiency is based on cortical hypertrophy and hypersecretion. Evidence of increased cortical secretion was also obtained in experiments on humans in which the influence of high altitude flying was reproduced. The adrenals react similarly with increased secretion if either the supply of oxygen is reduced or the body's demand for oxygen is increased. The cortical hormone acts as a catalytic agent in the activation of enzyme systems. The secretion of the adrenal medulla cooperates in the maintenance of tissue respiration, which thus appears as the function of the adrenal gland as a whole rather than that of the cortex alone.

BERNSTEIN

HYPERTENSION

Zollinger, H. U.: Pathogenesis and Pathologic Anatomy of Hypertension. Schweiz. med. Wchnschr. **80:** 533 (May), 1950.

On the basis of an analysis of anatomic findings in experimental and clinical hypertension the author presents a concept of the pathogenesis of the disease. The main pathologic changes are found in the arterioles in the form of arteriolosclerosis or arteriolonecrosis. Both are variations of the same pathogenetic principle, namely penetration and infiltration of the walls of the vessels by plasma constituents, effected by the high intravascular pressure. According to this concept, hypertension precedes and produces arteriolosclerosis. The latter is seen in older subjects, in which the process takes place slowly and without disturbing the continuity of the different layers of the vessel wall. In younger individuals the infiltration occurs more rapidly with disruption of the structure of the vessel, thus leading to arteriolonecrosis (malignant sclerosis). The author reports two observations in which the primary renal origin of hypertension was proved by a fall of blood pressure following extirpation of a diseased kidney.

PICK

Hegglin, R.: The Medical Treatment of Essential Hypertension. Schweiz. med. Wchnschr. **80:** 545 (May), 1950.

The author presents a survey of the effectiveness of various forms of medical treatment of essential hypertension. Adjustment and organization of the patient's activities and relaxation, supported by sedation (barbiturates), is essential. A salt free diet with 0.5 Gm. of sodium chloride a day produced no better effect than a salt poor diet containing 3 to 4 Gm. of sodium. Maintenance of Kempner's diet over several weeks is, in the author's experience, difficult and may lead to unpleasant symptoms, especially severe headaches. Treatment by thiocyanate requires regular control of the blood levels, which should not exceed 8 to 12 mg. per cent, to avoid unpleasant side effects of the drug. A new sympathicolytic drug, Hydergin (a mixture of three ergot alkaloids), may relieve symptoms without effecting a fall of blood pressure. Vitamin A may have some effect, especially if used in a less purified form. Vitamin K can be tried in view of its inhibitory effect on cholinesterase. Both tetraethylammonium and Dibenamine are unsuitable for a prolonged treatment of hypertension since their effect on the blood pressure is only transient and unpleasant side effects are not rare. The author feels that biologic methods, which should be developed in the future, will be more successful in the treatment of hypertension than methods available at the present.

PICK

Wertheimer, P.: Adrenalectomy in Hypertension. Lyon chir. **45:** 417 (May–June), 1950.

The author divides hypertension into two classes. The first is renal, in which renal ischemia results in the production of renin, which changes into angiotonin in the presence of hypertensin. He feels that adrenaline is necessary to sensitize tissues to renin and other products of the ischemic kidney. The second classification is endocrine, in which adrenal stimulation and the production of adrenaline under pituitary control is believed to be the important factor. Thirty-two adrenal glands removed from hypertensive patients all showed pathologic changes.

The author studied 22 cases of hypertension on which unilateral (left) adrenalectomy was performed. Of the 22 cases, 5 involved adrenalectomy alone, the other 17 included splanchnicectomy, unilateral or bilateral lumbar sympathectomy, decapsulation, or denervation of the renal capsule. The cases were followed from 2½ to 15 years. Eight of the patients died within a period of 8 years; 3 more were followed up inadequately; of the remaining 13, 8 showed good results (no functional disturbance or hypertension), and 5 showed poor results. The author advocates unilateral adrenalectomy with sympathectomy in the treatment of hypertension.

BERRY

Perera, G. A., Fleming, T. C., Pines, K. L., and Crymble, M.: Cortisone in Hypertensive Vascular Disease. J. Clin. Investigation **29:** 739 (June), 1950.

A 37 year old woman with uncomplicated hypertensive vascular disease (admission blood pressure 210/128) was given 50 mg. of cortisone acetate every 6 hours for 30 days. Clinical effects included insomnia, increased appetite, increased loss of scalp hair, and delayed healing of a superficial pyogenic abscess. Cortisone administration induced negligible fluid, electrolyte or carbohydrate changes. There was a marked negative nitrogen balance and a fall in serum potassium and cholesterol concentrations. The renal plasma flow decreased, and there was an apparent small decline in cardiac output. Following a preliminary rise, there was a small decline in "resting" blood pressure (from 146/106 to 134/93). This persisted for several weeks after the steroid had been discontinued.

WAIFE

Kert, M. J., Rosenberg, M. J., Coodley, E. L., Murdock, L. J., Hoffman, S. H., Brotman, E. J., and Johnston, W. L.: Treatment of Hypertension. J. A. M. A. **143:** 721 (June), 1950.

The authors report a study of 59 hypertensive patients treated with a diet containing approximately 200 mg. of sodium but adequate in other respects. Thirty-six patients were able to adhere strictly to the diet. Seventeen adhered to it moderately well, and 6 followed it poorly. Twenty-five per cent of the patients had significant drops in blood pressure; approximately 45 per cent of these patients also had significant weight loss. Decided improvement or complete relief from headaches was reported by 87 per cent of these patients. The 5 patients in this series who had papilledema improved. The patients with diminished renal function seemed to tolerate the diet well and improved in both their hypertensive status and renal function. The diet, reported in detail, is probably easier to follow than the rice and fruit juice diet, but, because of the large variety of foods allowed, the physician is less certain of the strict reduction of sodium.

KITCHELL

PATHOLOGIC PHYSIOLOGY

Harford, C. G., and Hara, M.: Pulmonary Edema in Influenzal Pneumonia of the Mouse and the Relation of Fluid in the Lung to the Inception of Pneumococcal Pneumonia. J. Exper. Med. **91:** 245 (March 1), 1950.

The authors report studies indicating that pulmonary edema is a component of the influenza viral lesion in the mouse and that the presence of fluid in the lungs is an important factor in the inception of pneumococcal pneumonia in this animal. In addition, it is shown that the chief action of fluid under these circumstances is to furnish a culture medium for growth of pneumococci and apparently decrease the phagocytic efficiency of leukocytes and macrophages.

Pulmonary edema was induced in mice either by administering sterile normal mouse serum intrabronchially or by inoculating alpha naphthyl thiourea intraperitoneally. The latter in lethal doses has a selective effect on the capillaries of the lung, rendering them permeable to plasma proteins. Although conditions in mice are not strictly comparable to those in humans, it is likely that pulmonary fluid is an important factor in susceptibility to pneumonia in humans. In this connection conditions complicated by pulmonary edema, such as congestive heart failure and shock, are known to be associated frequently with secondary bacterial pneumonia.

SCHWARTZ

Brauch, F.: Trigeminus Heart Reflex in Cardiovascular Disease. Zschr. f. Kreislaufforsch. **39:** 130 (March), 1950.

Immersion of the face in cold water (+10 C.) is followed by certain reflexes mediated over the trigeminal nerve to the cardiovascular system and to the centers for respiration. The author followed the changes seen in the electrocardiograms of normal persons and of patients with cardiovascular disease. In normal persons he observed transient bradycardia with appearance of A-V nodal escape. In about one third of cases with various heart diseases (myocardial damage following an infectious disease, arteriosclerotic heart disease with and without myocardial infarction), the transient sinus bradycardia

was very marked and sometimes accompanied by transient first degree A-V block, ventricular premature beats, and bigeminy. In another smaller group with a "fixed heart rate" (thyrotoxic heart disease, coronary sclerosis) no reaction was seen. In some cases (thermosensible stenocardiacs), the appearance of changes in the electrocardiogram could be correlated with the appearance of subjective symptoms. The author recommends the immersion test for clinical use in the recognition of reflex sensitivity of the cardiovascular system.

PICK

Corelli, D.: Experimental Studies on Renal Circulation. Ischemia of the Kidney following Injection of Histamine. Schweiz. med. Wchnschr. **80:** 552 (May), 1950.

The author reports his observations on kidney circulation in rabbits following the injection of 0.12 to 0.25 mg. of histamine. Injection into the aorta produced a contraction of both the renal artery and vein lasting seven to ten seconds. During this period different stages of kidney ischemia could be demonstrated by a rapid injection of india ink into the aorta. The results were less obvious when histamine was injected into a peripheral vein or into the renal parenchyma. The ischemia could be completely abolished by a synthetic antihistamine (3277 RP).

PICK

Langley, L. L., Nims, L. F., and Clarke, R. W.: Role of CO_2 in the Stress Reaction to Hypoxia. Am. J. Physiol. **161:** 331 (May), 1950.

In an effort to determine whether hypoxemia or hypocapnia is the more important factor in producing increased liver glycogen at high altitudes, a number of rats were exposed to 20,000 ft. atmosphere with and without added carbon dioxide. Fasting liver glycogen levels were approximately 0.5 per cent. If fasting rats were placed in 20,000 ft. atmosphere for 24 hours, the average liver glycogen levels were 3.6 per cent. If carbon dioxide at a pressure of 30 mm. Hg was added to the 20,000 ft. atmosphere, no increase in liver glycogen was found. Therefore, the authors conclude that liver glycogen accumulation at high altitude is more closely related to loss of carbon dioxide, a result of hypoxic hyperventilation, than to hypoxemia per se.

HECHT

White, A. G., and Sachs, B. A.: Studies in Edema: Cholesterol and Its Relation to Protein Nitrogen in Edema Fluid. Science **112:** 18 (July 7), 1950.

The edema fluid of 16 patients with congestive heart failure or venous and lymphatic obstruction was analyzed for cholesterol, cholesterol esters, and protein nitrogen. Similar determinations were performed on sera. The average cholesterol value of edema fluid was 14.6 mg. per cent in congestive heart failure, 17.3 mg. per cent in venous obstruction, but 175 mg. per cent in lymphatic obstruction.

WAIFE

PATHOLOGY

McKee, E. E.: Mycotic Infection of Brain with Arteritis and Subarachnoid Hemorrhage. Am. J. Clin. Path. **20:** 381 (April), 1950.

To the 5 previously reported cases of aspergillosis in which the brain was involved, the author adds another. The patient, a 60 year old man, complained of constant headaches localized to the left temporal region. No pathologic reflexes were noted. Repeated examinations of cerebrospinal fluid revealed from 60 to 331 cells, most of them polymorphonuclear leukocytes. The total protein varied from 121 to 190 mg. Spinal fluid cultures were repeatedly negative for bacteria, torula, or other fungi and yeasts. At autopsy there was an extensive subarachnoid accumulation of blood over the base of the brain and, to a lesser extent, over the left temporal and parietal lobes. Over the inferior surface of the frontal lobes there was a thick inflammatory membrane. Microscopic sections revealed focal areas of a caseous type of necrosis with numerous branching hyphae permeating these sites. The fungus was considered to be aspergillus, although it was admitted that identification of fungi in deep tissues is uncertain.

ABRAMSON

Wuhrmann, F.: Myocarditis—Myocardosis—Myocardie. Schweiz. med. Wchnschr. **80:** 715 (July), 1950.

Myocarditis and the syndrome of myocardosis are both cardiac manifestations of a generalized disease and can be distinguished only by the histologic picture. Myocarditis following bacterial or viral infection or in the course of an allergic disease presents the picture of a true cellular inflammation. Myocardosis, on the other hand, is characterized by "degenerative" changes of the myocardium (colliquation and disintegration of the fibrils, sarcolysis, and fatty infiltration of the myofibrils). These findings, which correspond to the "myocardie" of the French authors, can be found in chronic diseases of the kidney (nephrosis) or liver (cirrhosis), in comatose states (diabetes and uremia), in malignant diseases (especially multiple myeloma), during overwhelming infections (sepsis and diphtheria), in hormonal disturbances (Addison), in chronic intoxications (alcoholism), and following contusion of the chest. Dysproteinemia, common to most of the latter diseases, suggests that the histologic changes may be due to deposition of abnormal protein material in the myocardium. The electrocardiographic picture may be similar in both types of myocardial involvement (S-T anomalies, bundle branch block, Q-T prolongation). The correct diag-

nosis can sometimes be made following a detailed clinical and laboratory analysis.

PICK

Milne, J. A., Graham, J. G., and Simpson, J.: Cystic Mucoid Degeneration of the Aortic Media with Spontaneous Rupture of the Aorta. Glasgow Med. J. **31:** 206 (June), 1950.

A case is reported of a 24 year old woman, who without any premonitory symptoms, collapsed and remained unconscious for 30 minutes. Apart from extremely soft heart sounds and an unrecordable blood pressure, no abnormalities were found. In view of the low blood pressure, a diagnosis of adrenal apoplexy was considered, and the patient was given eucortone and desoxycorticosterone acetate. By the next day the patient had improved; her pulse was regular (110 per minute) and easily felt. The blood pressure was 130/90. On the second day after admission, further improvement was observed. Apart from a rather soft first heart sound, the patient seemed to be perfectly well. On the morning of the third day of hospitalization, the patient was found dead.

Necropsy findings: The pericardial sac was enormously distended with blood. In the intrapericardial portion of the aorta, the adventitia had ruptured and a large piece of fibrin protruded from the tear. On opening the heart, the first part of the aorta was seen to be dilated, and there was a linear tear 2½ inches in length running upwards and to the left from just above the posterior cusp.

The authors prefer to use the term cystic mucoid degeneration rather than cystic medionecrosis, because in this case and in photomicrographs of cases reported in the literature, the process is one of degeneration, there being no evidence of necrosis. The etiology of cystic mucoid degeneration is unknown.

GELFAND

PHARMACOLOGY

Kartun, P., Paris, P., Nory, J., and Bousquat, G.: Early Action on Venous Return of Intravenous Injections of a Mercurial Diuretic. Arch. d. mal. du Coeur **43:** 133 (Feb.), 1950.

The effect of the intravenous injection of a mercurial diuretic was studied by cardiac catheterization in 22 cases of rheumatic and hypertensive heart disease, cor pulmonale, and constrictive pericarditis. In most of the patients, the injection was followed by a rapid drop of pressure in the peripheral veins, right auricle, right ventricle, and pulmonary artery. The drop varied between 15 and 50 per cent. It was nearly constant in the presence of rheumatic and hypertensive disease, inconstant in cor pulmonale, and absent in constrictive pericarditis. The effects observed were attributed to a peripheral action of the mercurial diuretic. Treatment of paroxysmal dyspnea and acute pulmonary edema by means of mercurial diuretics is, therefore, advocated.

LUISADA

Nagakura, G.: Influence of Cold upon the Heart and Pupil, Both Denervated, in Dogs, before and after Demedullation of the Suprarenals. Tohoku J. Exper. Med. **50:** 39 (March), 1949.

The author denervated the eyes and hearts of dogs and applied a cold stimulus in the form of cold water introduced into the stomach through a stomach fistula. It was found that in dogs whose suprarenal glands had been demedullated, as well as in those not undergoing this operation, the application of cold resulted in both a paradoxical pupillary dilatation and an acceleration of the denervated heart. The pupillary reaction was found to occur in both operated and unoperated dogs more rapidly than the accompanying cardiac acceleration. However, the degree of pupillary dilatation was much less in the demedullated dogs. Demedullation apparently had no effect on the cardiac acceleration reaction. The author discusses the relationship of these findings to the rate and degree of epinephrine secretion.

SCHWARTZ

Hammerschmidt, D., and Odenthal, F.: The Effect of Hydrated Ergot Alkaloids on the Arterial and Venous Pressure. Ztschr. f. Kreislaufforsch. **39:** 150 (March), 1950.

The authors studied the changes in pulse rate and arterial and venous pressure produced in normotensive persons by intravenous infusion of various hydrated Secale alkaloids. Dihydroergotamine (DHE 45) in a dose of 0.5 to 1.0 mg. affected the systolic pressure insignificantly, but produced a rise in diastolic and venous pressure. This indicates a vasoconstrictive effect like that following injection of the genuine ergot alkaloids. Dihydroergocornine, dihydroergocristine, and dihydroergokryptine, in a dose of 0.5 mg., lowered systolic and diastolic pressure in the majority of cases without effecting changes in venous pressure. In some cases, with apparently higher sensitivity to vasoconstrictive impulses, an effect similar to that of DHE could be observed from each of the three drugs when injected separately. When given in a combination (CCK 179) in a dose of 0.3 mg., a fall of systolic and diastolic pressure was seen in most of the experiments. In none was there a rise in arterial pressure. This combination seems, therefore, most suitable for the treatment of essential and renal hypertension.

PICK

Duomarco, J., Rimini, R., De Bonnevaux, S. C., and Giambruno, C. E.: The Effect of Digitalis on Heart-Lung Preparations with Ventricular Strain.

Rev. argent. de cardiol. **17:** 65 (March-April), 1950.

The authors discuss the various theories offered to explain the action of digitalis and then describe the method used in their experiments. These consisted of 15 heart-lung preparations according to Knowlton and Starling's technic and a modification of Hoffmann's method for the optical recording of blood pressure and cardiac output. Heparinized blood of the same animal was used. The elastic peripheral resistance of the preparation was increased continuously and progressively. Oubain, "Arnaud," strophanthin Merck, and Digifoline Ciba were tested in widely divergent doses. Three conclusions were reached: (1) the therapeutic action of digitalis is not due to direct effect on the mechanical function of each contraction of the heart, be it increased contractility, prolonged diastole or both; (2) slowing of heart rate by digitalis, so characteristic in cardiac insufficiency, is not due to direct action on the myocardium, and (3) slowing of the heart is not due to a previous improvement of the mechanical function of the myocardium. These conclusions, especially the first one, do not agree with those of other authors who have also used similar heart-lung preparations.

SUÁREZ

Wollheim, E.: The Effect of Digitalis and Strophanthin on Hemodynamics. Deutsche med. Wchnschr. **75:** 483 (April), 1950.

The author studied the effect of intravenous injection of 2 cc. of Digipuratum of Digitalein (both corresponding to 0.2 Gm. of digitalis leaf) and of 0.25 mg. of K-strophanthin on circulation in normal subjects and in patients with heart disease. The latter included cases of hypertension, valvular disease, and chronic cor pulmonale with and without heart failure. Before and after injection of digitalis, circulating blood volume was determined by Evans blue, circulation time by the fluorescein or Decholin method, and venous pressure by the method of Moritz and Tabora. Digitalis as well as strophanthin diminished the circulating blood volume in all cases within 40 to 60 minutes. The venous pressure remained unchanged or decreased, the latter especially in cases with heart failure. The circulation time was shortened only in cases with heart failure. These observations are in accord with Starling's law.

The author suggests that the specific effect of digitalis is in the reduction of the circulating blood volume, which in turn decreases the input load on the heart and leads to an increase of cardiac output in the patient with heart failure. A direct effect on the venomotor system seems improbable. The main indication for use of digitalis is heart failure of any kind. No benefit can be expected of prophylactic digitalization in infections and preceding surgery in the absence of heart disease.

PICK

Douthwaite, A. H., and Finnegan, T. R. L.: Vasodilators in Peripheral Vascular Disease. Brit. M. J. 4658: 769 (April), 1950.

The authors studied the vasodilating effect of Priscoline on patients with vascular disorders, rheumatoid arthritis, and fibrositis. With an intravenous injection of 50 mg. of the drug, an increase of 6 to 7 C. was noted in the cutaneous temperature of the toes and a rise of 2 to 3 C. in the temperature of the fingers. In the patients with rheumatoid arthritis and fibrositis, some relief of stiffness of the joints was noted during the period of pharmacologic action. However, subsequent administration of the drug by mouth produced no noticeable benefit. The patients with Raynaud's disease responded quite favorably to the intravenous injection of Priscoline. There was an early flushing of the hands and fingers, lasting a minimum of eight hours and, in some instances, as long as one to two days. When the drug was subsequently given by mouth over extended periods of time, the side reactions were often quite marked and unpleasant. When the dose was reduced to the point of no longer producing these untoward effects, it failed to relieve the symptoms of Raynaud's disease. Intermittent claudication, due to arteriosclerosis obliterans, was helped by Priscoline in approximately half the patients. Night pain was abolished in the same cases. Trophic ulcers of the toes healed in 2 individuals following the use of the drug.

ABRAMSON

Diaz, F. V.: Atebrin in Paroxysmal Tachycardia and Paroxysmal Auricular Fibrillation. Brit. Heart J. **12:** 132 (April), 1950.

Atebrin was employed in 6 patients, 2 with paroxysmal tachycardia, 2 with paroxysmal auricular fibrillation, 1 with nodal tachycardia, and 1 with auricular flutter. The arrhythmia was terminated in 4 of the 6 patients. The author believes that atebrin has an anti-tachycardial and anti-fibrillatory action and is particularly effective in the presence of hypermetabolism. Atebrin is less toxic and has a wider margin of safety than quinidine.

SOLOFF

Pardo, E. G., Rennick, B. R., Moe, G. K.: A Cardiac Sympathetic Pathway Not Blocked by Tetraethylammonium. Am. J. Physiol. **161:** 245 (May), 1950.

In 8 intact dogs cardiac acceleration produced by stimulation of the preganglionic ramus was completely prevented by TEA for 10 to 20 minutes. Clamping the area of the sinus node abolished the blocking effect of TEA to preganglionic stimulation and cardiac acceleration; pacemaker shifts and the

rise in arterial pressure remained unaltered when compared to control values. Heart-lung-head preparations demonstrated that cardiac acceleration by bilateral occlusion of the carotids could be prevented by TEA when the sinus node had been clamped. Cephalic asphyxia, on the other hand, resulted in tachycardia which was again uninfluenced by TEA if the sinus region had been clamped.

TEA apparently fails to block the sympathetic inotropic and chronotropic effects on the A-V node and the ventricles. These impulses must reach the heart without synaptic transmission or proceed over synapses invulnerable to the action of TEA.

HECHT

Atanackovic, D., and Dalgaard-Mikkelsen, S.: Procaine and Autonomic Innervation. Proc. Soc. Exper. Biol. & Med. **74:** 55 (May), 1950.

Procaine paralyzes first the parasympathetic and later the sympathetic synapses. Procaine suppresses the nicotinic and muscarinic effects of acetylcholine on the heart, but not the muscarinic effect of acetylcholine on the blood vessels. Procaine curarizes first the intercostal respiratory muscles, then the diaphragm and finally the skeletal muscles. Physostigmine, dimethyl carbamate of hydroxyphenylbenzyltrimethylammonium (Nu-683) or diisopropyl fluorophosphate (DFP) suppress the paralyzing effects of procaine on synapses, on postsynaptic cardiac innervation, and on neuromuscular junctions, while procaine protects against most symptoms of intoxication produced by physostigmine, Nu-683 or DFP. The symptoms of intoxication produced by physostigmine, Nu-683 or DFP are bradycardia, bronchospasm, salivation, muscular fasciculations, and convulsions.

MINTZ

Goth, A., Holman, J., and O'Dell, V.: Effect of Mercurials on Kidney Adenosine Triphosphatase Activity. Proc. Soc. Exper. Biol. & Med. **74:** 178 (May), 1950.

Mersalyl and mercuric chloride were found to inhibit adenosine triphosphatase activity of homogenized rat kidneys. Following the intramuscular injection of various doses of Mersalyl into rats, renal adenosine triphosphatase activity was unchanged in 4 hours, but was decreased after 24 hours. Simultaneous microscopic and enzymic studies suggested that the decrease in adenosine triphosphatase activity was the result, and not the cause, of renal injury produced by Mersalyl.

MINTZ

Farnsworth, E. B.: Acute and Subacute Glomerulonephritis Modified by Adrenocorticotropin. Proc. Soc. Exper. Biol. & Med. **74:** 57 (May), 1950.

Two patients with subacute glomerulonephritis and one with rheumatic heart disease and acute glomerulonephritis were treated with adrenocorticotropin. The ACTH caused the hematuria to disappear in subacute glomerulonephritis or reduced it to an occasional erythrocyte, and the azotemia and hypertension were reduced. In one of these cases, hematuria recurred shortly after the discontinuation of the ACTH. In the other case, follow-up studies performed 8 months after treatment showed a normal blood pressure, absence of blood in the urine, but a slight increase in the blood urea and nonprotein nitrogen. It is concluded that hematuria, azotemia, and hypertension associated with active phases of glomerulonephritis can be favorably modified by ACTH.

MINTZ

Pordy, L., Arai, H. S., and Master, A. H.: Dihydroergocornine in the Differential Diagnosis of Functional Heart Disturbances and Organic Heart Disease. J. Mt. Sinai Hosp. **17:** 26 (May–June), 1950.

Twenty selected patients with signs and symptoms of cardiac disturbance were given the two step exercise test before and after the intravenous injection of dihydroergocornine (0.4 to 0.5 mg.). All 20 patients had previously had a positive two step exercise tolerance test, the electrocardiographic change being found most commonly in leads V_4 and II. Ten of the 20 patients were classified as functional heart cases, on the basis of clinical signs and symptoms; the remaining 10 as cases of definite organic heart disease. In all the functional cases, the RS-T and T-wave changes elicited by the two step exercise tolerance test could not be elicited by the same test 30 minutes after the intravenous injection of dihydroergocornine, whereas in the organic cases, these changes were unaffected by dihydroergocornine. The effects of dihydroergocornine on the electrocardiogram were not changed by preventing any postural hypotension that might occur with neosynephrine hydrochloride given intramuscularly. The authors believe that although the mode of action of dihydroergocornine is controversial, it appears to be a promising agent for the differentiation of functional and organic heart disease.

CORTELL

PHYSICAL SIGNS

Lian, C., Djordjevitch and Slavkovitch: Study of the Extra Sounds Caused by Diastolic Filling of the Ventricles. Arch. d. mal. du Coeur **43:** 141 (Feb.), 1950.

As a result of a clinical and phonocardiographic study of the diastolic extra sounds, the authors reach the following conclusions: (a) The third sound is due to increased activity in ventricular diastole. (b) The early-diastolic gallop is due to left ventricular failure followed by an increase of residual blood in the left ventricle. (c) Less severe failure is accompanied

by an auricular gallop. (d) Whenever more than one extra sound is present during diastole, the first is the loudest. (e) In A-V block, the first extra sound in diastole is a summation gallop and is louder than subsequent sounds. (f) The auricular sounds of the A-V block are frequently formed by two groups of vibrations. This is explained by the authors as being due to a greater amount of blood passing into the ventricles at the time of the auricular contraction.

In general, all extra sounds are explained by vibrations arising in the ventricular myocardium. Valvular vibrations may also be present, but they are of less importance.

LUISADA

Collens, W. S., Zilinsky, J. D., Boas, L. C., and Greenwald, J. J.: Impaired Vibratory Sense in Diabetes Mellitus with Proteinuria. J. Clin. Investigation **29:** 723 (June), 1950.

Using an electrically activated tuning fork for quantitating vibratory sense, the authors tested 200 diabetics, half of whom had proteinuria. Seventy-six per cent of proteinuric diabetics had vibratory sense impairment worse than 10 per cent normal. Only 2 per cent of the diabetics without proteinuria were as seriously affected. The factors of age, insulin requirements, and duration of the disease did not seem to play a part in these differences.

WAIFE

PHYSIOLOGY

Schwartz, I. L.: Measurement of Extracellular Fluid by Means of a Constant Infusion Technique without Collection of Urine. Am. J. Physiol. **160:** 523 (March), 1950.

A homogeneously dispersed substance occupying a fixed fraction of body water may allow estimation of the volume of fluid in which it has been distributed if the substance is rapidly diffusable. Under such conditions, if clearance is constant, removal of the substance from the bloodstream may be accomplished by extrarenal routes. For these determinations, no urine samples are necessary, and the volume of fluid may be calculated from the disappearance slope of the blood concentration. In other words, under conditions of total clearance, the volume of distribution of a rapidly diffusable substance is equal to the total clearance, divided by the decrement with time (slope) of the logarithm of the plasma concentration.

Using formulas derived from these considerations, space determinations were made for mannitol, thiosulfate, p-aminohippurate and T 1824. Mannitol space averaged 19 per cent of body weight in the dog, and 17 per cent in man. Thiosulfate space averaged 17 per cent in the dog. p-Aminohippurate space was calculated as 27 per cent in 2 dogs, and 29 and 26 per cent in man. T 1824 space in a human subject and in a dog measured 6 and 8 per cent respectively.

HECHT

Scow, J., Krasno, L. R., and Ivy, A. C.: The Immediate and Accumulative Effect on Psychomotor Performance of Exposure to Hypoxia, High Altitude and Hyperventilation. J. Aviation Med. **21:** 79 (April), 1950.

The exposure of 17 subjects to a simulated altitude of 18,000 feet without supplemental oxygen caused a deterioration of performance in the four psychomotor tests used: the flicker frequency fusion threshold, pursuitmeter, tremor, and tapping. Such exposure three times weekly for eight or nine weeks did not cause an objective deterioration in performance at ground level or high altitude. The subjects were definitely more irascible at high altitude toward the end of the experiment. Hyperventilation by 7 subjects just short of tetany for one hour every other day during 10 days did not yield evidence of an accumulative deterioration in performance. The exposure of 7 subjects to 35,000 ft., breathing 100 per cent oxygen, was not associated with a decrease in psychomotor performance, and no evidence of the accumulative effects of such exposure, three times a week for five weeks, was detected.

BERNSTEIN

Osher, W. J.: Change of Vital Capacity with the Assumption of the Supine Position. Am. J. Physiol. **161:** 352 (May), 1950.

Successive measurements of the vital capacity of 10 subjects in the supine position revealed that about 54 per cent of the mean loss of 341 cc. incident to the adoption of this position was regained in 10 minutes. The expiratory reserve likewise decreased a mean of 860 cc. but remained unchanged while the supine position was maintained. An increase in the vital capacity and a decrease of the expiratory reserve as compared with their previous erect values were found when the upright position was resumed. A high correlation between the vertical component of the arc through which the body moves in assuming the supine position and the diminution of the vital capacity was demonstrated in 6 subjects.

HECHT

Davies, D. F., and Shock, N. W.: Age Changes in Glomerular Filtration Rate, Effective Renal Plasma Flow, and Tubular Excretory Capacity in Adult Males. J. Clin. Investigation **29:** 496 (May), 1950.

Renal functions were studied in 70 ambulatory males between the ages of 20 and 90 years. All were free of evidence of renal and cardiac disease. The average inulin clearance, Diodrast clearance, and Diodrast Tm decreased linearly beyond the age of 30. The percentage decreases were 46, 53 and 43.5 per cent respectively. The filtration fraction rose

significantly between the third and ninth decades. The effective renal plasma flow decreased with increasing age.

WAIFE

RHEUMATIC FEVER

Good, R. A., and Glick, D.: Mucolytic Enzyme Systems. IX. Nonspecific Hyaluronidase Inhibitor in Rheumatic Fever. J. Infect. Dis. **86:** 38 (Jan.–Feb.), 1950.

A nonspecific inhibitor of hyaluronidase exists in the blood of normal and diseased individuals in addition to and distinct from specific antihyaluronidase antibody. In view of the possible role of hyaluronidase in the pathogenesis of rheumatic fever, the authors studied the alterations in the nonspecific hyaluronidase inhibitor in rheumatic fever. Sera from normal young adults, from normal children 1 to 15 years of age, and from children with active and inactive rheumatic fever, Sydenham's chorea, and streptococcus pharyngitis were studied.

The data indicated that the nonspecific hyaluronidase inhibitor in the sera of normal children does not differ significantly from that of healthy young adults. Marked increase of serum hyaluronidase inhibition was noted in the acute exudative phase of rheumatic fever. The elevation of inhibitor was apparently roughly proportional to the clinical severity of the exudative process of rheumatic fever, as indicated by the joint involvement, fever, sedimentation rate and carditis. Patients convalescent from rheumatic fever showed a lower concentration of inhibitor than normal healthy children. A similar finding was noted in children with inactive rheumatic fever. The mean value of serum hyaluronidase inhibitor found in patients with acute severe Sydenham's chorea was comparable to that obtained for the convalescent and inactive rheumatic fever patients. In the small series of cases of streptococcal pharyngitis studied, a wide variation of inhibitor levels was noted. Inhibitor was found to be elevated during the acute phase of bacterial infection; it returned promptly to normal levels as the infection subsided.

Although its lack of specificity limits the effectiveness of this test as a diagnostic procedure, it is concluded that the serum concentration of hyaluronidase inhibitor is a good index of the degree and duration of clinical rheumatic activity in many patients.

SCHWARTZ

Donzelot, E., and Kaufmann, H.: Heparin in the Treatment of Rheumatic Fever and Certain Inflammations. Arch. d. mal. du coeur **43:** 229 (March), 1950.

Fifteen cases of rheumatic fever were treated with heparin by intravenous injection. The authors suggest an important action of this substance on the protein balance of the blood. The useful action of heparin was revealed by the rapid reabsorption of fluid in cases of pleurisy or pericarditis and the decrease of dyspnea in cases of pulmonary congestion and pneumonia. The authors believe that heparin acts on the osmotic phenomena and discuss its action, comparing it with that of cortisone and ACTH.

LUISADA

Bywaters, E. G. L.: The Relation between Heart and Joint Disease Including Rheumatoid Heart Disease and Chronic Post-Rheumatic Arthritis (Type Jaccoud). Brit. Heart J. **12:** 101 (April), 1950.

The author re-examined the relationship between rheumatic fever and rheumatoid arthritis in the light of a thorough historical survey of the problem and of 27 instances of rheumatoid arthritis and of 4 instances of spondylitis ankylopoietica. He concludes that, by his criterion, the incidence of rheumatic fever is no higher in rheumatoid arthritis than in a control postmortem study. Three types of clinical relationships are present (1) rheumatoid arthritis with rheumatoid granulomata in the valve cusp and ring, frequently with pericarditis similar to the synovitis found in the affected joints (2) rheumatoid arthritis in an individual previously affected with rheumatic heart disease and (3) recurrent rheumatic fever with postrheumatic fibrous rheumatism originally described by Jaccoud. The deformity in this latter condition is characterized clinically by peri-articular swelling of the metacarpophalangeal joints with ulnar deviation and subluxation and pathologically by capsular swelling and intact synovial membrane; in the later stages bone and cartilage erosion may occur with characteristic hook-like deformity of the metacarpophalangeal heads.

SOLOFF

ROENTGENOLOGY

Dotter, C. T., and Jackson, F. S.: Death following Angiocardiography. Radiology **54:** 527 (April), 1950.

Twenty-six deaths have been reported from various sources in 6,824 angiocardiographic examinations (0.38 per cent). Twenty one occurred in patients with congenital heart disease; 17 of these were cyanotic. Seventeen deaths occurred in children under 8 years of age. One death occurred in a patient with renal arterial disease but with a normal heart. The commonest form of death was sudden respiratory arrest immediately or shortly after the injection of contrast substance. Subdural hemorrhage occured twice. The authors conclude that the nature of the contrast substance injected, the number of injections, premedication and general anesthesia did not significantly influence the mortality. The incidence of death, however, was highest in patients with congenital heart disease, in patients receiving larger doses of the contrast substance, and in those examined in the horizontal posture.

SCHWEDEL

Walti, J. J., and Nedey, R.: Abnormal Right Pulmonary Veins Diagnosed by Standard Roentgenology. Arch. d. mal. du Coeur **43:** 464 (May), 1950.

A syndrome in which some or all of the pulmonary veins drain into one of the cavae is now being encountered not infrequently. The authors report the case of a 6 year old patient in whom the right pulmonary veins drained into the inferior cava. A standard chest film revealed dextrocardia. It also revealed the existence of a vertical band of opacity at the right of the heart which was interpreted as a common venous collector for the right lung.

LUISADA

Axen, O. and Lind, J.: Table for Routine Angiocardiography. J.A.M.A. **143:** 540 (June), 1950.

The authors describe the application of a specially constructed table which permits the taking of synchronous serial roentgenograms in two planes at right angles, a method which is useful in angiocardiography. Ten pictures are taken within 5 to 10 seconds in the posteroanterior and lateral positions simultaneously. Depth as well as height and width may be estimated.

SCHWEDEL

Kreutzer, R. O., Caprile, J. A., and Wessels, F. M.: Angiocardiography in Heart Disease in Children. Brit. Heart J. **12:** 293 (July), 1950.

The authors describe their experience with angiocardiography in children and give illustrations of (1) the radiologic topography of the cardiovascular silhouette; (2) atelectasis of the right lung; (3) agenesis of the right lung; (4) tetralogy of Fallot and persistent ductus arteriosus; (5) tetralogy of Fallot with anomalous distribution of the vessels from the aortic arch; (6) persistent ductus arteriosus; (7) infundibular stenosis with dilated pulmonary artery; (8) coarctation of the aorta; (9) Taussig's syndrome, and (10) mediastinal tumor. The authors regard this procedure as that which gives the most valuable information in the diagnosis of congenital heart disease during infancy.

SOLOFF

SURGERY IN HEART AND VASCULAR SYSTEM

Randall, W. C., Alexander, W. F., Hertzman, A. B., Cox, J. W., and Henderson, W. P.: Functional Significance of Residual Sympathetic Pathways following Verified Lumbar Sympathectomy. Am. J. Physiol. **160:** 441 (March), 1950.

The authors studied vasomotor and sudomotor activity of the large central pad of the hind paw in 11 trained dogs before and at daily intervals for several weeks after a unilateral sympathectomy from the level of L-1 to L-7. High blood flows and surface temperatures established after operation declined significantly within two to seven days. The sweating response remained reduced.

Accessory vasoconstrictor fibers in the sympathectomized limb were demonstrated by direct faradic stimulation of the tibial and peroneal nerves which induced strong vasoconstriction in the footpad. Procaine blockade of these nerves resulted in prompt vascular relaxation. It is suggested that in these experiments recovery of vasomotor tone in the sympathectomized limbs was related to these accessory fibers. At autopsy, careful dissection of the spinal nerves and the intercommunicating rami of the lumbar segments revealed ganglion cell aggregates whose postganglionic fibers may pass directly along the ventral primary ramus without entering the paravertebral ganglion chain. These cells and their fibers would not be interrupted by lumbar ganglionectomy and may, therefore, provide an anatomic basis for the observed residual vasoconstrictor activity.

HECHT

Platt, R., and Stanbury, S. W.: Sympathectomy in Hypertension. Lancet **1:** 651 (April), 1950.

The authors discuss the results of surgery performed on some 80 hypertensive patients, many of whom were followed for two to three years. They state that surgical procedure failed to relieve the hypertension in many. They also feel that satisfactory results previously reported by others could be attributed to insufficient control, failure to observe the blood pressure for a sufficient time before surgery, failure to appreciate the great variability of blood pressure in the benign hypertensive patients, and ignorance of the natural history of the benign type of hypertension and its relatively good prognosis in milder cases. The authors are of the opinion that the height of blood pressure is not necessarily an accurate index to the severity of the basic disease processes, nor an infallible guide to prognosis. They also feel that even in those with very high pressures, including the young age group, there is little to suggest that sympathectomy in any way alters or reverses the basic disease process of which hypertension is but one effect.

Various types of operations were undertaken, and the group constituted all adult age categories and both sexes. Only cases with resting diastolic blood pressures of 120 mm. Hg. or more were included. In only 11 of the 80 cases was a significant and lasting reduction of blood pressure achieved. Most of these were young women under 40, suffering from either essential hypertension or from renal hypertension with good renal function. In some, headaches and retinopathy was occasionally relieved without reduction of blood pressure.

The author concludes that great care should be taken in choosing subjects for sympathectomy and that the operation should rarely be advised.

TANDOWSKY

THROMBOEMBOLIC PHENOMENA

McClelland, C. Q., and Hughes, J. P.: Thrombosis of the Renal Vein in Infants. J. Pediat. **36:** 214 (Feb.), 1950.

The authors present 3 cases of thrombosis of the renal vein with renal infarction, and discuss their clinical and pathologic features. These cases were encountered among 328 consecutive autopsies performed on full-term infants who survived at least 24 hours after delivery but died before 12 months. Thrombosis of the renal vein in infants causes a rarely diagnosed syndrome, characterized by sudden onset of hematuria or anuria, shock, and the appearance of palpable lateral abdominal masses in an infant usually suffering from dehydration as a result of severe diarrhea. Characteristic urinary findings consist of gross or microscopic hematuria or hemoglobinuria with varying degrees of associated pyuria, cylindruria, and albuminuria.

Several factors tend to render the veins of the kidneys susceptible to thrombosis in infants. The precariousness of the water balance in the neonatal period, the initial physiologic weight loss plus the onset of diarrhea may favor intravascular clotting. The nature of the renal circulation with its double capillary network results in slowing of the blood in the renal veins and may account for their predominance as a site of thrombosis. The large intrarenal veins are the most likely vessels initially involved in thrombosis.

Both excretory and retrograde urographic studies are important in arriving at the correct diagnosis. The greatest hope for recovery lies in prompt surgical intervention with nephrectomy following an early diagnosis. Anticoagulant therapy may be beneficial in postoperative management.

SCHWARTZ

Jones, R. S., Black, T. C., and Sparr, H. A.: Incidence and Significance of Thromboembolism in Pulmonary Tuberculosis. Am. Rev. Tuberc. **61:** 826 (June), 1950.

The authors studied the incidence of thromboembolism in 60 patients who died with pulmonary tuberculosis. They found that in 11 cases this condition was present, but in only one was the embolism associated with pulmonary infarction. None of the patients in the series showed any significant cardiac disease or chronic passive congestion of the lungs. Nine of the 11 patients were over 40 years of age. In most of the cases, the emboli had lodged in the pulmonary arteries supplying the tissue least involved by tuberculosis. This relationship may have been due to the fact that the lower lobes are frequently the sites of emboli, while being the least frequent site of tuberculosis. Another possibility is that there is an increased blood flow through the remaining uninvolved lung in severe pulmonary tuberculosis.

As a result of the tendency to occlude the pulmonary arteries of the good pulmonary tissues, the thrombotic emboli can sometimes produce death even when only a single lobar artery is affected. The mechanism of death would appear to be the mechanical occlusion of blood flow through the pulmonary arteries, thus decreasing cardiac output and reducing aeration of blood.

ABRAMSON

VASCULAR DISEASE

Lampen, V. H., and Wadulla, H.: Syphilitic Aortitis with the Clinical Picture of "Reversed Coarctation of the Aorta." Deutsche med. Wchnschr. **75:** 144 (Jan.), 1950.

The author describes two cases of syphilitic aortitis (one of which was autopsied) with marked narrowing of the ostia of the large vessels at their origin in the arch of the aorta. The main symptoms were attacks of dizziness and fainting. At physical examination very small pulses were found in the upper part of the body while hypertension was present in the lower extremities. This syndrome is called by the authors "reversed coarctation of the aorta." The elevation of the blood pressure in the legs could have been due to a loss of elasticity of the wall of the aorta or to a reflex vasoconstriction in periphery effected by pressoreceptors in the carotid arteries, where the blood pressure was low. An additional factor could have been an insufficient blood supply to centers in the diencephalon, which control the circulation.

PICK

Scheuer-Karpin, R.: Report on a Case of Periarteritis (Polyarteritis) Nodosa. Ztschr. f. d. ges. Inn. Med. **5:** 65 (Feb.), 1950.

A 43 year old woman with a history of bronchial asthma, urticaria and Quincke's edema was admitted to the hospital with lobar pneumonia and developed the following symptoms: persistent tachycardia; transient elevation of the blood pressure with attacks of unconsciousness and convulsions; a peculiar glossitis which resembled the "surface of a kidney with infarcts"; myalgias and transient peritoneal symptoms; anemia, leukocytosis and a marked increase of the sedimentation rate; unilateral retinitis with hemorrhage; hematuria and cylindruria. The patient died on the seventh day of observation with symptoms of acute encephalitis. The clinical diagnosis of polyarteritis nodosa was confirmed at autopsy which revealed the typical changes in the arterioles, especially in the kidneys and in the tongue.

PICK

Searles, P. W., and Nowill, W. K.: Cerebral Vascular Accidents: Treatment by Stellate Ganglion Blocks. South. M. J. **43:** 229 (March), 1950.

The authors discuss the common cerebral vascu-

lar lesions and their usual treatment as well as the technic and indications for stellate ganglion block. A group of 55 patients with cerebral vascular lesions on whom 127 stellate ganglion blocks were performed were compared with a control series of 158 similar patients. Best results with stellate ganglion block were obtained in cases of cerebral thrombosis of recent origin. Forty-five per cent of 31 treated patients showed improvement as compared with 19 per cent of 89 patients in a control group. The mortality rate was 35 per cent in the treated group as compared with 58 per cent in the controls. There was also evidence of some improvement in cases of cerebral embolism as well as in chronic cerebral thrombosis treated by ganglion block.

SCHWARTZ

OTHER SUBJECTS

Schoenmackers, J.: The Distribution of the Veins of the Heart. Ztschr. f. Kreislaufforsch. **39:** 68 (Feb.), 1950.

The author studied the distribution of the venous system of the heart by injecting radiopaque material into the coronary sinus. He found one type of heart in which all veins drained into the sinus and another type in which, in addition, some of the veins opened into the right auricle or ventricle. Only some of the superficial veins followed the distribution of the coronary arteries. Normally, the density of the venous system is greater over the left ventricle; it is especially so with hypertrophy of this chamber, when the vessels also become larger and wider. The veins over a parietal aneurysm remained unfilled, if injection was tried from the coronary sinus or from the arterial side. The author describes an observation of a "blind" sinus venosus without any opening into the auricles. A secondary sinus was present in this case, draining into the left auricle.

PICK

Kisch, B.: Reflex Cardiac Inhibition in the Ganoid Acipenser Sturio. Am. J. Physiol. **160:** 552 (March), 1950.

The electrocardiogram of a sturgeon was recorded by the author's technic. Touching the aperture of the mouth, palate, oral cavity, or gills resulted in temporary standstill of the heart, as did touching of the eyeballs, barbels, or fins. Touching or pressing the tail had no ostensible reflex effects.

HECHT

Bouvrain, Y., and Bescol-Liversac, M.: Anatomic, Roentgenologic, and Histiologic Study of Calcifications of the Cardiac Openings. Arch. d. mal. du coeur **43:** 189 (April), 1950.

Both atherosclerosis and rheumatic fever may be followed by calcification of the cardiac rings and valves. According to the authors, atherosclerosis is followed most frequently by calcification of the aortic valve, causing stenosis. On the other hand, rheumatic fever is followed most often by calcification of the mitral valve and fibrotic fusion of the aortic leaflets. The usual sequence is sclerosis, necrosis, caseation, calcification, and, occasionally, ossification.

LUISADA

Berman, L., Axelrod, A. R., Goodman, H. L., and McClaughry, R. I.: So-called "Lupus Erythematosus Inclusion Phenomenon" of Bone Marrow and Blood. Am. J. Clin. Path. **20:** 403 (May), 1950.

Recent studies provide useful adjuncts to the diagnosis of acute disseminated lupus erythematosus. These consist of the observation of certain phenomena in smears of centrifuged, heparinized, oxalated or citrated blood, or marrow of diseased patients. The phenomena include (a) leukocytes containing ingested masses of cloudy structure, presumably mostly of nuclear origin, which vary in density and staining reaction (LE cells); (b) free, non-phagocytozed masses identical with those in LE cells, and (c) clusters of neutrophiles about masses of cellular debris. Similar changes are rare or absent in other types of lupus erythematosus, in conditions related to the so-called collagen disease group, or in unrelated conditions.

Plasma from patients with acute lupus erythematosus is capable of provoking the appearance of the LE phenomena when added to suspensions of marrow cells from normal persons, patients with various diseases, and various laboratory animals. Serum obtained post mortem retains a similar activity. The activity of LE plasma appears to reside in the gamma globulin fraction. The authors also discuss the technic for an in vitro test for the LE factor.

BEIZER

Southworth, J. L., McKusick, V. A., Peirce, E. C., and Rawson, F. L.: Ventricular Fibrillation Precipitated by Cardiac Catheterization. J. A. M. A. **143:** 717 (June 24), 1950.

The authors report a case of ventricular fibrillation precipitated by cardiac catheterization, which was done to determine the presence or absence of left or right shunt. While the tip of the catheter was in the right ventricular cavity, the patient suddenly went into ventricular fibrillation. The cardiac catheter was withdrawn into the vena cava, and resuscitative measures were instituted. Incision was made and manual cardiac compression begun. Between the fifteenth and fortieth minutes following onset, five electric shocks were administered to the heart with a defibrillating apparatus. After the fourth electric shock, 20 cc. of 1 per cent procaine hydrochloride solution was injected directly into the heart. After the fifth shock 2 cc. of 1 per cent lidocaine hydrochloride (xylocaine hydrochloride) in

epinephrine hydrochloride (1:100,000) was injected directly into the left ventricle. Following this, a sixth shock of 135 volts of one second's duration with electrodes on the precordium and ventricular pericardium induced a transitory reversion to something resembling normal rhythm. Five cc. of 1 per cent lidocaine-epinephrine was then injected directly into the left ventricular cavity. The seventh shock of 135 volts (one and one-half seconds' duration) was followed by sinoauricular rhythm. Ventricular fibrillation lasted 45 minutes. Oxygen was given by nasal catheter for the following three days, in addition to large doses of penicillin and streptomycin.

KITCHELL

BOOK REVIEWS

The Practice of Medicine, ed. 5. *Jonathan Campbell Meakins.* St. Louis, The C. V. Mosby Co., 1950. 1558 pages, 518 figures, $13.50.

The fact that five editions of this textbook have appeared since 1936 is adequate testimony to its value. The subject matter is presented fully and an explanation of abnormal signs and symptoms is given as far as possible from the point of view of pathologic physiology, although sufficient organic pathology is included to cover this aspect of the various diseases.

The clarity of the discussion will be a great help in giving the student a logical understanding of the various processes. Furthermore, the book is beautifully and profusely illustrated so that these two features make it much easier to read than the average textbook on general medicine.

The section on cardiovascular disease is excellent and one of the most complete in any treatise of this nature. This is to be expected because of the author's long interest in the subject. Any practitioner or student who has acquainted himself with the facts presented and the advice given will assuredly practice a fine sort of cardiology. As heart disease is the most important cause of edema, it might be well to transfer this to the cardiovascular section and to have its physiology discussed by the author in rather more detail. It might be well also, in dealing with coronary occlusion, to show in the electrocardiograms multiple precordial leads and also the unipolar limb leads, since these have assumed so much importance of late.

Undoubtedly this is one of the outstanding books on the practice of medicine at present and can be most thoroughly recommended to all internists and students.

J. HAMILTON CRAWFORD

Akute Infektionskrankheiten und Hochdruck. *Otto Heinrich Arnold.* Georg Thieme Verlag, Stuttgart, 1949. 130 pages, $2.30.

The author's main thesis is that vascular disease in general, and hypertensive vascular disease in particular, are a consequence of infectious disease. In his opinion, proper recognition of this would, at least to a certain extent, result in the prevention of the development of the chronic, progressive vascular disease and the hypertension. Adequate therapy, such as rest, baths, graded exercise, and occasionally, restriction of salt in the diet, would prevent irreparable damage to the circulation.

The cause of progression of the vascular disease still remains as obscure as its mechanism. The injurious influence of focal infections has, in the author's opinion, been exaggerated, and he does not know of a case of his own in which the removal of the focus resulted in an unequivocal cure. He lays greater stress upon the susceptibility of the diseased individual to stimuli rather than upon the nature or strength of the stimulus. For this reason he believes that sympathectomy is the only form of therapy that has been directed toward the modification of the sensitivity of the host to pathologic stimuli. He believes that personal and individual factors determine whether, as a consequence of an infection (such as scarlet fever or streptococcic sore throat), acute nephritis, purpura hemorrhagica, myocarditis, serositis, vascular disease, or some other pathologic process will appear. He sees in the previously existing infection an etiologic relationship between a great variety of disease processes that develop later. Ever and always, he stresses the individual reactions of the patient which he believes are even phylogenetically determined and limited. He cites the well known fact that, in the case of acute rheumatic fever, endocarditis almost invariably develops in the young, whereas it rarely occurs in individuals who have an attack of rheumatic fever for the first time after their thirtieth year. All through the book the author gives illustrative examples of clinical cases in which, after a variable period following an infection of some type, hypertensive or some other

form of vascular disease develops. He states that the disease which accounts for the development of the largest number of cases of disturbance of the circulatory system later is scarlet fever. Among the other infectious diseases which predispose to the development of vascular disease, he lists diphtheria, tonsillitis, influenza, rheumatic fever, typhus, and even malaria and pneumonia. These cases demonstrate that during the infection a fleeting hypertension may develop, which may become more manifest later, and persist. He admits that various types of vascular disease may originate from various causes but contends that differentiation on this basis cannot always be made at present. The book is a good summary of the author's views.

HARRY GOLDBLATT

Die physikalische Analyse des Elektrokardiogramms vom gesunden und kranken Herzen. *Lothar Wendt.* Leipzig, Georg Thieme, 1946. 347 pages, 129 figures, $9.60. **Die Ermittlung des Erregungsablaufs in ungeschädigten und geschädigten Herzen durch Analyse des Elektrokardiogramms und des Vektordiagramms.** *Lothar Wendt.* Berlin, Akademie-Verlag. 1949. 84 pages, 29 figures.

Both books are concerned mainly with the analysis of the vectors at the peaks of the QRS complex and T wave and during the S-T segment of the electrocardiogram. The author's views and interpretations are unorthodox, to say the least, and, for the greater part, are palpably wrong. Because the vector at the peak of QRS is roughly directed from the basis to the apex, Wendt assumes that the excitation spreads that way. He denies that the excitation spreads from the endothelial to the epicardial surface or that the initial QRS deflection has any relationship to septum activation. Repeating Wilson's experiments, he was unable to record negative potentials when the electrode pierced the ventricular wall to the endocardial surface but did not enter the cavity.

Unfortunately, Wendt's interpretation is mainly based on his faulty assumption of the pathway of excitation, though this is not the only source of misinformation. Nevertheless, his apparently large experimental material should not be ignored, the more so as some of his results are not easily compatible with current assumptions. For instance, in some of his experiments in cats and dogs the Q wave decreased markedly in magnitude when the area of lesion was extended from the lateral wall of the left ventricle to include finally about half the area of the anterior wall.

The value of vector analysis of the S–T segment for the localization of recent lesions, especially for differentiation of basis and apex lesions, is illustrated. Although more recent and more complete material is now available (American Heart Journal **36**: 184, 1948), Wendt's results are still of interest. He found the S-T vector always directed towards the site of the lesion. Consequently, a lesion in the center of the heart may show no significant S-T deviations, and two opposite lesions (for instance base and apex) of similar magnitude may also produce cancellation of S-T deviations so far as the projection onto the standard leads is concerned. However, the error of measurement in the vector analysis of the S-T deviation must be quite large unless the deviations are extreme, and this leaves some question about the significance of his results.

In general, Wendt's lack of understanding of statistical evaluation is regrettable; nowhere are numbers of experiments, normal limits or distribution, or any statistical analyses of clinical material given. Since only selected cases are presented, one would like to know how representative these cases are. Furthermore, the clinical material is only occasionally supported by autopsy evidence.

Perhaps the most interesting part of the books is the application of new leads, although Wendt did not bother to obtain normal standards for these. Wendt's procedure consists in placing on the chest wall around the heart nine anatomically defined points. Points 1-4-7 correspond to the Einthoven triangle, point 1 being near the right shoulder, point 4 near the left shoulder, and point 7 between the ensiform and umbilicus. Points 2, 3, 5, 6, 8, and 9 are equally spaced between points 1, 4, 7 and 1. Derivation from a triangle 2-5-8 would be equivalent to a left axis shift, and using the triangle 9-3-6 would be equivalent to a right axis shift. It is possible, therefore, to bring a heart with an abnormal position into a nearly normal positional reference in regard to one or the other of Wendt's triangles. Although the triangles are most likely not equilateral nor the electrodes equidistant from the heart, this procedure, as illustrated in numerous figures in various types of lesions, is conceivably valuable for differentiation between lesions and positional changes. In addition to the frontal triangles a sagittal triangle is used, defined by the following points: right arm electrode at the manubrium, left leg electrode at the xiphoid process, left arm electrode on the back at a level halfway between the right arm and left leg electrode. This triangle is not equilateral; however, the direction of the vector and its approximate magnitude can be estimated. The sagittal triangle is used especially for posterior wall lesions.

Another suggestion of possible merit is a bipolar precordial lead parallel to the electrical axis, connecting roughly the base and apex. It is shown that this lead may magnify or even bring out certain abnormalities, especially S-T deviations, which are often less favorably projected on to other leads.

In view of the time of publication (1946) of the first book, the quality of the paper and illustrations is surprisingly good, but the book would have gained by condensation. Such condensation is given in the second book, in addition to the graphical construc-

tion of complete vectordiagrams. The limitations and advantages of electrocardiograms and vectordiagrams are discussed, and an attempt is made to differentiate several abnormal patterns of vectordiagrams in different lesions (hypertrophy, bundle branch block, infarct). So far as vectordiagrams are concerned, the information given is of preliminary nature, and in part superseded by Duchosal and Sulzer's recent monograph (La vectocardiographie, S. Karger, Basel, 1949).

ERNST SIMONSON

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ACTH AND CORTISONE STUDY

An international cooperative study of the effectiveness of the hormone substances ACTH and cortisone in the treatment of rheumatic fever and the prevention of rheumatic heart disease is being conducted under the auspices of the American Council on Rheumatic Fever of the American Heart Association. Six research centers in the United States, one in Canada, and five in Great Britain have agreed to cooperate in the rheumatic fever study in order to provide enough experience in the use of the hormones to obtain conclusive results in the shortest possible time.

Dr. David D. Rutstein, Professor of Preventive Medicine, Harvard Medical School, is Chairman of the Committee on Criteria and Standards of the American Council on Rheumatic Fever, which has had the responsibility for planning and organizing the study and which will supervise and coordinate the investigations of the twelve research centers. Patients treated during acute attacks of rheumatic fever during the next calendar year will be followed for at least three years. Investigators in the United States and Canada will report their findings to the New York coordinating center, where analysis will be made. These findings will be compared with results obtained by a special committee of the British Medical Research Council.

Grants have been made by the National Heart Institute of the U. S. Public Health Service to help finance the coordinating center and principal investigators of cooperating research centers in New York, Boston, Denver and Chicago. In addition, the Armed Forces Epidemiological Board and the United States Air Force will finance a cooperating research center at the Francis E. Warren Air Force Base in Wyoming. A research center in Toronto, Ontario, has been financed by the Canadian Rheumatism and Arthritis Foundation. In England, the individual research centers and the Medical Research Council are financing the studies.

Armour & Co., which produces ACTH, and Merck & Co., which produces cortisone, have already contributed the sum of $5,000 each to pay for the planning of the study, and will contribute the large amounts of hormone agents necessary to conduct the investigation.

Early promising results in the treatment of rheumatic fever with the two hormones have indicated the need to determine whether or not these agents actually alter the course of rheumatic fever or merely suppress the symptoms, and whether they prevent rheumatic heart disease. The availability of hormone agents that are difficult to administer and control and that may result in unfortunate side effects has accented the need for special study in research centers where results can be carefully evaluated. The information on diagnosis, treatment, and follow-up to be collected in this study should be useful to specialists and general practitioners.

The cooperating research centers and principal research investigators at each center are as follows: New York University-Bellevue Medical Center (including Irvington House), New York, Dr. Currier McEwen; College of Physicians and Surgeons, Columbia Univer-

sity, New York, Dr. Edward E. Fischel; House of the Good Samaritan, Boston, Dr. Benedict F. Massell; Francis E. Warren Air Force Base, Fort Warren, Wyoming, and Western Reserve University, Cleveland, Dr. Charles H. Rammelkamp; University of Colorado, Denver, Dr. Harry H. Gordon; University of Chicago (including Jackson Park Sanitarium), Dr. Albert Dorfman; Hospital for Sick Children, Toronto, Canada, Dr. John D. Keith; British Medical Research Council, Sir James Spence (Chairman, ACTH-Cortisone Committee of the Rheumatic Fever Panel), Dr. Eric G. L. Bywaters (Secretary, ACTH-Cortisone Committee of the Rheumatic Fever Panel). The British centers are located at Newcastle, London, Taplow, Cardiff and Sheffield.

1951 HEART FUND

Bruce Barton, Chairman of the Board of the advertising firm of Batten, Barton, Durstine & Osborn, will serve as Chairman of the 1951 Heart Fund drive which will be conducted throughout February. The slogan of the fund campaign will be "New Hope for Hearts," to call attention to the scientific gains achieved in the cardiovascular field. American Heart Week is scheduled for February 11–18.

Charles E. Wilson, President of General Motors Corporation, will serve as Campaign Vice-Chairman of the Heart Fund. Winthrop Aldrich, Chairman of the Board of the Chase National Bank, will once again be campaign Treasurer. Committee heads include Secretary of Labor Maurice J. Tobin, Chairman, Labor Committee; Assistant Secretary of the Interior C. Girard Davidson, Chairman, Federal Employees Committee; and Arthur Pryor, Jr., Vice-President, Batten, Barton, Durstine & Osborn, Chairman, Radio and Television Committee.

AMERICAN SOCIETY FOR STUDY OF ARTERIOSCLEROSIS

Dr. E. Cowles Andrus, Baltimore, a member of the Scientific Council and Board of Directors of the American Heart Association, has been installed as President of the American Society for the Study of Arteriosclerosis. Dr. G. Lyman Duff, Montreal, was chosen Vice-President, and Dr. O. J. Pollak, Quincy, Mass., was re-elected Secretary-Treasurer.

COOK COUNTY HOSPITAL FELLOWSHIPS

The Pediatric Cardiology Department of the Children's Division of the Cook County Hospital is now accepting applications for fellowships for immediate appointment. The department offers large material of both congenital and acquired diseases of the heart. There is a complete department of angiocardiography and catheterization. Salary will be commensurate with experience.

Further information may be obtained from Dr. Rowine H. Brown, Assisant Medical Superintendent Children's Division of the Cook County Hospital 700 South Wood Street, Chicago 12, Ill.

AMERICAN JOURNAL OF THE MEDICAL SCIENCES

Starting with the January 1951 issue of the American Journal of the Medical Sciences, the new Editor is Dr. Richard A. Kern, Professor and Head of the Department of Medicine, Temple University School of Medicine, Philadelphia. The new Associate Editor is Dr. Thomas M. Durant, Professor of Clinical Medicine at Temple, and the new Assistant Editor is Dr. Chris J. D. Zarafontis, Associate Professor of Internal Medicine at the same school. These men will succeed the former editorial board headed by Dr. E. B. Krumbhaar of the University of Pennsylvania, who has retired after twenty-five years of association with the Journal.

GERONTOLOGICAL CONGRESS

The Second International Gerontological Congress will be held at the Hotel Jefferson, St. Louis, Mo., September 9–14, 1951. The program will include sections on Biology and Medicine; and Medical Services, Hygiene and Housing. The Chairman of the Program Committee is Dr. John Esben Kirk, Washington University Medical School, 5600 Arsenal Street, St. Louis 9, Mo.

VOLUME II INDEX

Your attention is called to the complete volume index published with the December, 1950, issue. Your comments will be appreciated.

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*Overman, W. J.; Gordon, W. H., and Burch, G. E.: Tracer Studies of the Urinary Excretion of Radioactive Mercury following administration of a Mercurial Diuretic, Circulation *1*:496, 1950.

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Circulation

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The JOURNAL of the AMERICAN HEART ASSOCIATION

CONTENTS